

**ADENOSINE DERIVATIVE AND PHARMACEUTICAL COMPOSITION
COMPRISING THE SAME**

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial No. 62/879,414, filed July 27, 2019, which is herein incorporated by reference in its entirety.

FIELD

[0002] This disclosure is directed to adenosine derivative prodrugs that can inhibit reverse transcriptase. This disclosure is also directed to pharmaceutical compositions comprising an adenosine derivative prodrug that can be used for the treatment of acquired immunodeficiency syndrome (AIDS), HIV-1, HIV-2, multidrug resistant HIV or a combination thereof.

BACKGROUND

[0003] Retroviruses such as human immunodeficiency virus (HIV) has been linked to the immunosuppressive disease known as acquired immunodeficiency syndrome (AIDS). Multiple strains of retrovirus, such as HIV type-1 (HIV-1) and type-2 (HIV-2) are known to be related to the diseases. The HIV retrovirus infected individuals can be initially asymptomatic, but then develop AIDS related complex (ARC) followed by AIDS. Replication of HIV by a host cell requires integration of the viral genome into the DNA of host cells. A key step in the process involves transcription of the viral RNA genome into DNA via an enzyme known as reverse transcriptase (RT).

[0004] A reverse transcriptase typically can have multiple enzymatic functions that can act (1) as an RNA-dependent DNA polymerase transcribing a single-stranded DNA copy of the viral RNA (first DNA), (2) as a ribonuclease destroying the original viral RNA and frees the DNA just produced from the original RNA, and (3) as a DNA-dependent DNA polymerase producing a second, complementary DNA strand using the first DNA strand as a template. The two DNA strands then form double-stranded DNA, which is integrated into the genome of the host cells by an integrase enzyme.

[0005] A number of compounds can inhibit reverse transcriptase (RT) activity. These compounds can be useful for the treatment of HIV infection in humans by inhibiting HIV replication in infected cells or individuals. Examples of the compounds approved for use in treating HIV infection and AIDS include nucleoside RT inhibitors (NRTI) such as 3'-azido-3'-deoxythymidine (AZT, also known as Zidovudine (ZDV), azidothymidine (AZT)), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), d4T, 3TC, abacavir, emtricitabine, and tenofovir disoproxil fumarate, as well as non-nucleoside RT inhibitors (NNRTI) such as nevirapine, delavirdine, efavirenz, rilpivirine and doravirine (DHHS guidelines: <https://aidsinfo.nih.gov/understanding-hiv-aids>, Iyidogan & Anderson, *Viruses*, 6, 4095-4139, 2014, doi:10.3390/v6104095; Hayakawa et al., *Antiviral Chem & Chemotherapy*, 15:169-187, 2004; Ohrul et al., *J. Med. Chem.* 43, 4516-4525, 2000; Pauwels, *Antiviral Research*, 71, 77-89, 2006.).

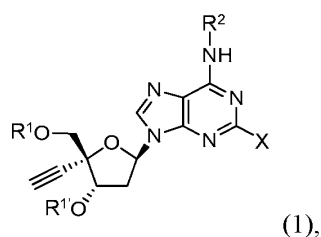
[0006] An adenosine derivative EFdA (4'-ethynyl-2'-fluoro-2'-deoxyadenosine, also known as MK-8591, islatravir) is a long-acting (LA) NRTI that has been demonstrated to have anti-HIV activity via inhibiting reverse transcriptase by preventing translocation (U.S. Patent Nos.: 7,339,053, 7,625,877, 8,039,614. Singh et al., *Pharmaceuticals*, 12, 62, 2019, DOI: 10.3390/ph12020062, each of which is incorporated by reference herein in its entirety). This compound has broad inhibitory activity and potency for different subtypes and mutations including HIV-1, HIV-2, and multidrug resistant (MDR) and wildtype (WT) strains, and reverse transcriptase inhibitor (RTI) resistant viruses. Some modified EFdAs and prodrugs have been described in U.S. Patent Publication No.: 2018/0002366, incorporated by reference herein in its entirety.

[0007] A common issue that arises from the treatment of HIV infection with anti-retroviral inhibitory compounds is resistance of the viruses to the inhibitors. Such resistance is typically the result of mutations that occur in the reverse transcriptase segment of the *pol* gene. The continued use of antiviral compounds, such as the inhibitory compounds, to prevent HIV infection will inevitably result in the emergence of new resistant strains of HIV. Therefore, there is a continuing need for new RT inhibitors that are effective against HIV strains including mutant HIV and multidrug-resistant HIV strains.

SUMMARY

[0008] The present disclosure is related to adenosine derivatives and compositions thereof that can be used to treat retroviral diseases such as HIV and AIDS.

[0009] In some embodiments, the present disclosure provides an adenosine derivative or stereoisomer, pharmaceutically acceptable salt, tautomer, or solvate thereof having a formula (1):

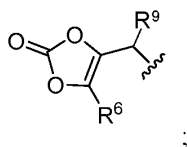


wherein,

R^1 , $R^{1'}$, and R^2 each is independently -H, -C(O)N(R^3)($R^{3'}$), -C(O)OR⁴, -R⁵, -L¹-R⁵, or -Z-L⁴-R⁵, wherein at least one of R^1 and R^2 is not -H;

R^3 , $R^{3'}$ and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, or heteroaryl;

R^5 is:



R^6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

-L¹-R⁵ is -(C1-C10 alkylene)-N(R^7)-R⁵, -(C1-C10 alkylene)-O-R⁵, -(C1-C10 alkylene)-S-R⁵, -(C2-C10 alkenylene)-N(R^7)-R⁵, -(C2-C10 alkenylene)-O-R⁵, -(C2-C10 alkenylene)-S-R⁵, -C(O)O-R⁵, -C(O)O-L²-N(R^7)-R⁵, -C(O)O-L²-O-R⁵, -C(O)O-L²-S-R⁵, -C(O)O-L²-C(O)O-R⁵, -C(O)O-L²-C(O)N(R^7)-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-N(R^7)-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-O-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-S-R⁵, -

C(O)N(R⁷)-R⁵, -C(O)N(R⁷)-L²-N(R⁷)-R⁵, -C(O)N(R⁷)-L²-O-R⁵, -C(O)N(R⁷)-L²-S-R⁵,
-C(O)N(R⁷)-L²-C(O)O-R⁵, -C(O)N(R⁷)-L²-C(O)N(R⁸)-R⁵-, -C(O)N(R⁷)-L²-
C(O)N(R⁸)-L³-N(R⁷)-R⁵, -C(O)O-L²-N(R⁷)C(O)O-R⁵, -C(O)N(R⁸)-L²-N(R⁷)C(O)O-
R⁵, -C(O)O-L²-N(R⁷)C(O)N(R⁸)-R⁵, -C(O)N(R⁷)-L²-N(R⁷)C(O)N(R⁸)-R⁵, -
C(O)N(R⁷)-L²-C(O)N(R⁸)-L³-O-R⁵ or -C(O)N(R⁷)-L²-C(O)N(R⁸)-L³-S-R⁵.

-Z- is a divalent -C(O)-, -C(O)O-, or -C(O)N(R⁷)-;

-L⁴-R⁵ is -(C1-C10 alkylene)-N(R⁷)-R⁵, -(C1-C10 alkylene)-O-R⁵, -(C1-C10 alkyl)-S-R⁵, -(C2-C10 alkenylene)-N(R⁷)-R⁵, -(C2-C10 alkenylene)-O-R⁵ or -(C2-C10 alkenylene)-S-R⁵;

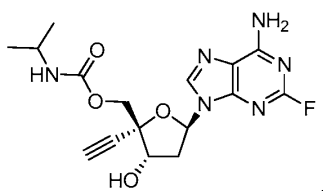
R⁷, R⁸ and R⁹ each is independently -H, C1-C10 alkyl, or C2-C10 alkenyl;

L² and L³ each is -(C1-C10 alkylene)-, or -(C2-C10 alkenylene)-; and

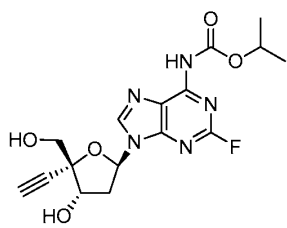
X is a halogen atom.

[00010] In some embodiments, the adenosine derivative is selected from the group consisting of:

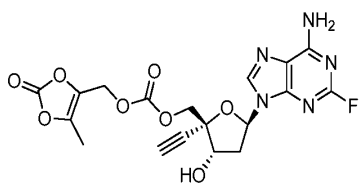
formula (2-A):



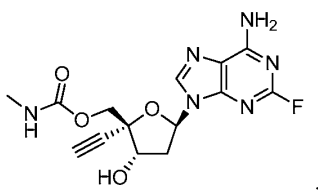
formula (3-A):



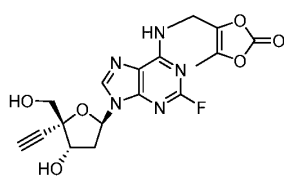
formula (4-A):



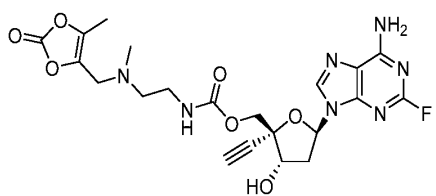
formula (5-A):



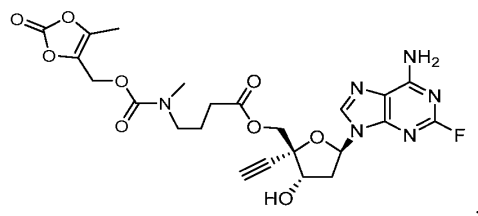
formula (6-A):



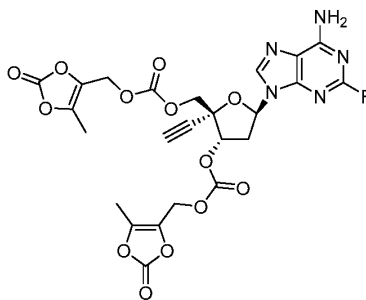
formula (7-A):



formula (8-A):

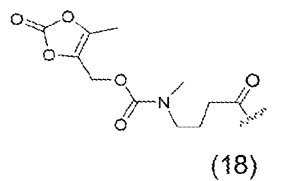
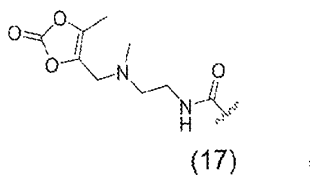
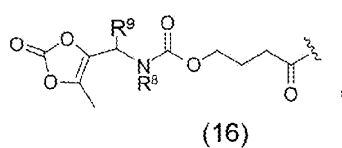
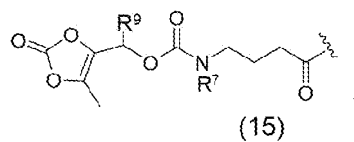
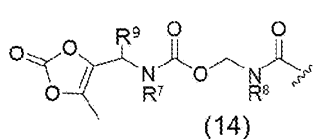
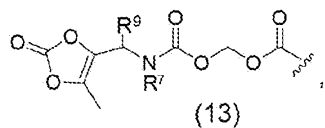
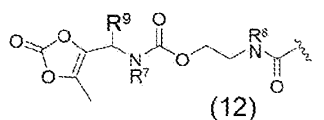
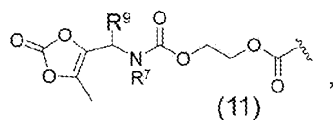
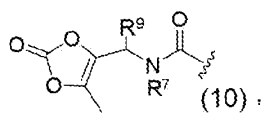
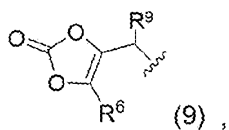


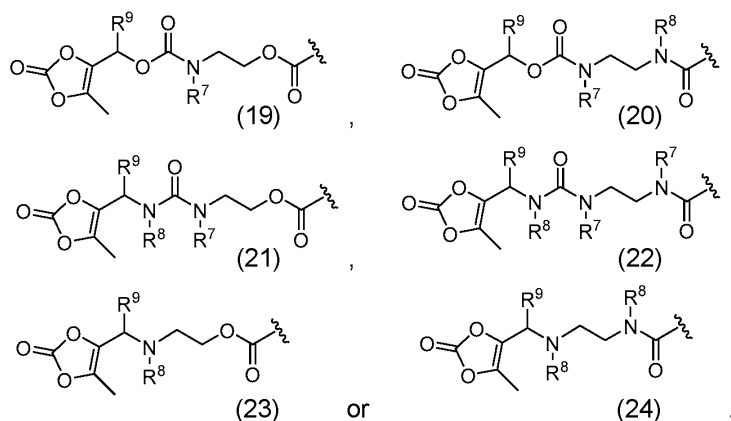
formula (4-C):



or a stereoisomer, pharmaceutically acceptable salt, tautomer, or solvate thereof.

[00011] In some embodiments of formula (1), the adenosine derivative comprises an R^1 , $R^{1'}$, R^2 or a structure selected from formulas 9 – 24:





[00012] The present disclosure is further directed to a pharmaceutical composition comprising one or more adenosine derivatives, pharmaceutically acceptable salts, stereoisomers, or a combination thereof disclosed herein, and one or more pharmaceutically acceptable carriers.

[00013] The present disclosure is also directed to a method for the treatment of a disease (e.g., Acquired Immune Deficiency Syndrome (AIDS) or human immunodeficiency virus (HIV)), the method comprising administering to a subject in need thereof an effective dosage of a pharmaceutical composition comprising one or more of the adenosine derivatives disclosed herein.

[00014] The present disclosure is also directed to a method for the prevention of infection, the method comprising administering to a subject in need thereof an effective dosage of a pharmaceutical composition comprising one or more of the adenosine derivatives disclosed herein.

INCORPORATION BY REFERENCE

[00015] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[00016] **Fig. 1A – Fig. 1I** show exemplary chemical structures of adenosine derivatives having a halogen atom with formulas (1) – (8) and 4-B.

[00017] **Fig. 2A – Fig. 2I** show exemplary chemical structures of adenosine derivatives having a fluorine atom with formulas (1-A) – (8-A) and 4-C.

[00018] **Fig. 3A – Fig. 3J** show exemplary chemical structures of the -R⁵, -L¹-R⁵ or -Z-L⁴-R⁵ groups of the adenosine derivatives with formulas (9) – (18).

[00019] **Fig. 4A – Fig. 4F** show exemplary chemical structures of the -L¹-R⁵ or -Z-L⁴-R⁵ groups of the adenosine derivatives with formulas (19) – (24).

[00020] **Fig. 5A – Fig. 5B** show exemplary chemical structures of 4'-ethynyl-2-halogen-2'-deoxyadenosine (Fig. 5A, formula (T-1)) and 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) (Fig. 5B, formula (T-1A)).

DETAILED DESCRIPTION

[00021] Following are more detailed descriptions of various concepts related to, and embodiments of, methods and apparatus according to the present disclosure. It should be appreciated that various aspects of the subject matter introduced above and discussed in greater detail below may be implemented in any of numerous ways, as the subject matter is not limited to any particular manner of implementation. Examples of specific implementations and applications are provided primarily for illustrative purposes.

[00022] As used herein, the term “alkyl” or “alkyl group” refers to a fully saturated, straight or branched hydrocarbon chain having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C₁-C₁₂ alkyl, an alkyl comprising up to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls and C₁ alkyl (*i.e.*, methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl

includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted..

[00023] As used herein, the term “alkylene” or “alkylene chain” refers to a fully saturated, straight or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C₁-C₁₂ alkylene include methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[00024] As used herein, the term “alkenyl” or “alkenyl group” refers to a linear or branched chain aliphatic hydrocarbon radical containing at least one carbon-carbon double bond and having a number of carbon atoms in the specified range. For example, “C₂-C₁₀ alkenyl” (or “C₂-C₁₀ alkenyl”) refers to any of alkenyl having 2 to 10 carbon atoms that is linear or branched, or isomers. In another example C₂-C₆ alkenyl can have 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl). The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[00025] As used herein, the term “alkenylene” or “alkenylene chain” refers to an unsaturated, straight or branched divalent hydrocarbon chain radical having one or more olefins and from two to twelve carbon atoms. Non-limiting examples of C₂-C₁₂ alkenylene include ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the

alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain can be optionally substituted.

[00026] As used herein, the term “cycloalkyl” refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon consisting solely of carbon and hydrogen atoms, which can include fused or bridged ring systems, having from three to twenty carbon atoms (e.g., having from three to ten carbon atoms) and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. In some embodiments, “cycloalkyl” refers to any monocyclic ring of an alkane having a number of carbon atoms in the specified range. For example, “C3-C10 cycloalkyl” (or “C₃-C₁₀ cycloalkyl”) refers to monocyclic ring of an alkane having 3 to 10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[00027] As used herein, the term heterocycloalkyl,” “heterocyclic ring” or “heterocycle” refers to a saturated, or partially saturated 3- to 20-membered ring which consists of two to nineteen carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and which is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, the heterocycloalkyl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocycloalkyl can be optionally oxidized, e.g., to form an *N*-oxide, sulfoxide, or sulfone and/or the nitrogen atom can be optionally quaternized, e.g., to form a quaternary ammonium cation. Examples of such heterocycloalkyls include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholyl, 1-oxo-thiomorpholyl, and

1,1-dioxo-thiomorpholinyl. In some embodiments, “3- to 10- membered heterocycloalkyl” refers to a cycloalkyl comprising one or more heteroatoms, selected from the group consisting of N, O, and S. In some embodiments, heterocycloalkyl,” “heterocyclic ring” or “heterocycle” refers to a 3-10 member ring structure having carbon atoms and one or more heteroatoms selected from N, O, S or a combination thereof as members of the ring structure. Unless stated otherwise specifically in the specification, a heterocycloalkyl group can be optionally substituted and include saturated and/or unsaturated rings.

[00028] As used herein, the term “halogen” (or “halo”) refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (-F), chloro (-Cl), bromo (-Br), and iodo (-I)).

[00029] As used herein, the term “aryl” refers to a hydrocarbon ring system comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the aryl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryls include, but are not limited to, aryls derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In some embodiments, “aryl” refers to phenyl or one or more fused cyclic hydrocarbon ring systems in which at least one ring is aromatic. Unless stated otherwise specifically in the specification, the “aryl” can be optionally substituted.

[00030] As used herein, the term “heteroaryl” refers to a 5- to 20-membered ring system comprising hydrogen atoms, one to nineteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the heteroaryl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl can be optionally oxidized, e.g., to form an *N*-oxide, sulfoxide, or sulfone and/or the nitrogen atom can be optionally quaternized, e.g., to form a quaternary ammonium cation. Non-limiting examples of heteroaryls can include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl,

thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl triazolyl (i.e., 1,2,3-triazolyl or 1,2,4-triazolyl), tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl (i.e., the 1,2,3-, 1,2,4-, 1,2,5-(furazanyl), or 1,3,4-isomer), oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Suitable 9- and 10-membered heterobicyclic, fused ring systems include, for example, benzofuranyl, indolyl, indazolyl, naphthyridinyl, isobenzofuranyl, benzopiperidinyl, benzisoxazolyl, benzoxazolyl, chromenyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, tetrahydro uinolyl, tetrahydroisoquinolinyl, isoindolyl, benzodioxolyl, benzopiperidinyl, benzisoxazolyl, benzoxazolyl, chromanyl, isochromanyl, benzothienyl, benzofuranyl, imidazo[1,2-a]pyridinyl, benzotriazolyl, dihydroindolyl, dihydroisoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalyl, quinazolinyl, 2,3-dihydrobenzofuranyl, and 2,3-dihydrobenzo-1,4-dioxinyl. Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[00031] It is understood that, unless expressly stated to the contrary in a particular context, any of the various cyclic rings and ring systems described herein may be attached to the rest of the compound at any ring atom (i.e., any carbon atom or any heteroatom) provided that the attachment is chemically allowed.

[00032] As used herein, the term “substituted” means any of the groups described herein (*e.g.*, alkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, heterocyclyl, and/or heteroaryl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkylarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (*e.g.*, a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, “substituted” includes any of the above groups in which one or more hydrogen atoms are replaced

with $-\text{NR}_g\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{OR}_h$, $-\text{NR}_g\text{SO}_2\text{R}_h$, $-\text{OC}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{OR}_g$, $-\text{SR}_g$, $-\text{SOR}_g$, $-\text{SO}_2\text{R}_g$, $-\text{OSO}_2\text{R}_g$, $-\text{SO}_2\text{OR}_g$, $=\text{NSO}_2\text{R}_g$, and $-\text{SO}_2\text{NR}_g\text{R}_h$. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced with $-\text{C}(=\text{O})\text{R}_g$, $-\text{C}(=\text{O})\text{OR}_g$, $-\text{C}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{CH}_2\text{SO}_2\text{R}_g$, $-\text{CH}_2\text{SO}_2\text{NR}_g\text{R}_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. “Substituted” further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

[00033] As used herein, the term “isomer” refers to a structural isomer, such as a group or an atom positioned at different locations of a molecule; stereoisomer, such as a chiral isomers, enantiomers, diastereomers and cis/trans isomers; a tautomer, such as amino isomer, imino isomer, or a combination thereof. In non-limiting examples, an adenosine derivative of the present disclosure can have an amino isomer, an imino isomer or a combination thereof. In another non-limiting example, in instances where an -OH substituent is permitted on a heteroaromatic ring and keto-enol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the oxo ($=\text{O}$) form. A mixture of isomers can also be suitable. A mixture of isomers can comprise the respective isomers in all ratios. A salt of an isomer can also be suitable. An adenosine derivative of the present disclosure can comprise isomers thereof, one or more salts thereof, one or more solvates including hydrates thereof, solvated salts thereof or a mixture thereof. Absolute stereochemistry or isomer configuration may be determined by X-ray crystallography, by Vibrational Circular Dichroism (VCD) spectroscopy analysis or a combination thereof.

[00034] The adenosine derivatives can be identified by names based on the nomenclature recommended by International Union of Pure and Applied Chemistry

(IUPAC) or based on nucleosides (Nucleoside-based nomenclature). The adenosine derivatives can also be identified by chemical structure drawings. Unless expressly stated to the contrary in a particular context, the names and the structures may be used interchangeably.

[00035] Any of the atoms in a compound disclosed herein may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure is meant to include all suitable isotopic variations of the compounds disclosed herein.

[00036] The compounds can be administered in the form of pharmaceutically acceptable salts or solvates. The term "pharmaceutically acceptable salt" refers to a salt or a solvate which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient or subject thereof). A mixture of a compound disclosed herein and one or more salts or solvates thereof is also contemplated herein. Illustrative examples of pharmaceutically acceptable salts include, but are not limited to, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrate, citrates, lactates, γ -hydroxybutyrate, glycolates, tartrates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

[00037] Furthermore, compounds disclosed herein can exist in amorphous form and/or one or more crystalline forms, or a combination thereof.

[00038] The term "RNA virus infection" refers to a disease caused by an RNA virus, such as the common cold, influenza, SARS, COVID-19, hepatitis C, hepatitis E, West Nile fever, Ebola virus disease, rabies, polio, and measles.

[00039] The term “HIV infection” refers to a disease caused by the human immunodeficiency virus (HIV), such as HIV-1 and HIV-2. In some cases, the HIV infection can be caused by wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV. The term “AIDS” refers to acquired immunodeficiency syndrome, which is caused by HIV infection and an advanced form of the disease.

[00040] The term “prodrug” refers to a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term “prodrug” refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be a biologically inactive or substantially inactive compound which can be metabolized in the body, i.e., in vivo, to produce a drug having a desired activity. The term “substantially inactive” means that a prodrug can have about 1% to about 10% of the activity of the corresponding drug or after being metabolized in vivo, percentage based on weight of the prodrug. In some embodiments, the term “substantially inactive” means that a prodrug has less than about 5% of the activity of the corresponding drug or after being metabolized in vivo, percentage based on weight of the prodrug. The doses for a prodrug and its biologically active compound are considered to be does-equivalent when they are the same molar amount.

[00041] The term “anti-HIV agent”, “anti-viral agent” or a grammatical variant refers to a compound, a mixture of one or more compounds, a formulation, a chemical agent or a biological agent such as antibody, protein, peptides, nucleotide, other biological compound, or a combination thereof, that can be directly or indirectly effective in the inhibition of HIV, the treatment or prophylaxis of HIV infection, and/or the treatment, prophylaxis or delay in the onset or progression of AIDS and/or diseases or conditions arising therefrom or associated therewith, an RNA virus infection, or a combination thereof. The anti-HIV agents can comprise HIV antiviral agents, immunomodulators, anti-infectives, vaccines or a combination thereof useful for treating HIV infection or AIDS. Examples of antiviral agents for Treating HIV infection or AIDS include, but are not limited to, under respective trademarks or registered trademarks with respective owners, abacavir (ABC, Ziagen®), abacavir + lamivudine (Epzicom®), abacavir + lamivudine + zidovudine (Trizivir®), amprenavir

(Agenerase®), atazanavir (Reyataz®), AZT (zidovudine, azidothymidine or Retrovir®), capravirine, darunavir (Prezista®), ddC (zalcitabine, dideoxycytidine or Hivid®), ddi (didanosine, dideoxyinosine or Videx®), ddi (enteric coated, Videx EC®), delavirdine (DLV or Rescriptor®), dolutegravir (Tivicay®), doravirine (MK-1439), efavirenz (EFV, Sustiva®, Stocrin®), efavirenz + emtricitabine + tenofovir DF (Atripla®), EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine), elvitegravir, cabotegravir, dolutegravir, bictegravir, emtricitabine (FTC, Emtriva®), emtricitabine + tenofovir DF (Truvada®), emvirine (Coactinon®), enfuvirtide (Fuzeon®), enteric coated didanosine (Videx EC®), etravirine (TMC-125), fosamprenavir calcium (Lexiva®), indinavir (Crixivan®), lamivudine (3TC, Epivir®), lamivudine + zidovudine (Combivir®), lopinavir, lopinavir + ritonavir (Kaletra®), maraviroc (Selzentry®), nelfinavir (Viracept®), nevirapine (NVP, Viramune®), PPL-100 (also known as PL-462) (Ambrilia), raltegravir (MK-0518 or Isentress™), rilpivirine (Edurant®), ritonavir (Norvir®), saquinavir (Invirase®, or Fortovase®), stavudine (d4T, didehydrodeoxythymidine or Zerit®), tenofovir DF (DF=disoproxil fumarate, TDF, Viread®), Tenofovir (hexadecyloxypropyl (CMX-157), Tenofovir alafenamide fumarate (GS-7340), tipranavir (Aptivus®) and vicriviroc. Some of the anti-HIV agents shown above can be used in a salt form; for example, abacavir sulfate, delavirdine mesylate, indinavir sulfate, atazanavir sulfate, nelfinavir mesylate, saquinavir mesylate or other salts. An anti-HIV agent can have one or more activities such as entry inhibitor (EI), fusion inhibitor (FI); integrase inhibitor (InI); protease inhibitor (PI); nucleoside reverse transcriptase inhibitor (NRTI or NRTI) or non-nucleoside reverse transcriptase inhibitor (nnRTI or NNRTI). An anti-HIV agent can comprise two or more agents disclosed herein. The adenosine derivative of the present disclosure can be an anti-HIV agent along or in combination with other anti-HIV agent or agents.

[00042] Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaryl ring described as comprising in a range of from "1 to 4 heteroatoms" means the ring can comprise 1, 2, 3 or 4 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, 3 heteroatoms, or 4

heteroatoms. In other examples, C1-C10 alkyl means an alkyl comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 carbon atoms including all sub-ranges. Thus, a C1-C10 alkyl can be a methyl, ethyl, C4 alkyl, C5 alkyl, C6 alkyl, C7 alkyl, C8 alkyl, C9 alkyl and C10 alkyl, linear or branched. A divalent C1-C10 alkyl can be a -CH₂-, -C₂H₄-, -C₃H₆-, -C₄H₈-, -C₅H₁₀-, -C₆H₁₂-, -C₇H₁₄-, -C₈H₁₆-, -C₉H₁₈- or -C₁₀H₂₀-, linear or a branched. Similarly, C2-C10 alkenyl means an alkenyl comprises 2, 3, 4, 5, 6, 7, 8, 9 and 10 carbon atoms, linear or branched, including all sub-ranges. A linear or a branched alkenyl can be suitable. A C3-C10 cycloalkyl means a cycloalkyl comprises 3, 4, 5, 6, 7, 8, 9 and 10 carbon atoms, linear or branched.

[00043] Unless otherwise indicated, open terms for example “contain,” “containing,” “include,” “including,” and the like mean comprising.

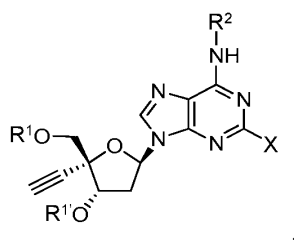
[00044] The singular forms “a,” “an,” and “the” are used herein to include plural references unless the context clearly dictates otherwise. Accordingly, unless the contrary is indicated, the numerical parameters set forth in this application are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

[00045] The term “about” and its grammatical equivalents in relation to a reference numerical value and its grammatical equivalents as used herein can include a range of values plus or minus 10% from that value, such as a range of values plus or minus 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% from that value. For example, the amount “about 10” includes amounts from 9 to 11.

[00046] The pharmaceutical composition can be suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active ingredient can be coated in a material to protect it from the action of acids and other natural conditions that may inactivate it. The phrase “parenteral administration” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. Alternatively, the

pharmaceutical composition can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, *e.g.*, intranasally, orally, vaginally, rectally, sublingually or topically. The pharmaceutical composition can be in the form of sterile aqueous solutions or dispersions. The pharmaceutical composition can also be formulated in a microemulsion, liposome, or other ordered structure suitable to high drug concentration.

[00047] In some embodiments, the present disclosure provides an adenosine derivative or a pharmaceutically acceptable salt, tautomer, or solvate thereof, having a formula (1):

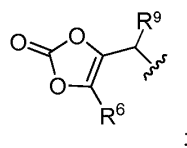


wherein,

R^1 , $R^{1'}$, and R^2 each is independently -H, -C(O)N(R^3)($R^{3'}$), -C(O)OR⁴, -R⁵, -L¹-R⁵, or -Z-L⁴-R⁵, wherein at least one of R^1 and R^2 is not -H;

R^3 , $R^{3'}$ and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

R^5 is:



R^6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, or heteroaryl;

-L¹-R⁵ is -(C1-C10 alkylene)-N(R^7)-R⁵, -(C1-C10 alkylene)-O-R⁵, -(C1-C10 alkylene)-S-R⁵, -(C2-C10 alkenylene)-N(R^7)-R⁵, -(C2-C10 alkenylene)-O-R⁵, -(C2-C10 alkenylene)-S-R⁵, -C(O)O-R⁵, -C(O)O-L²-N(R^7)-R⁵, -C(O)O-L²-O-R⁵, -C(O)O-

L^2-S-R^5 , $-C(O)O-L^2-C(O)O-R^5$, $-C(O)O-L^2-C(O)N(R^7)-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-N(R^7)-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-O-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-S-R^5$, $-C(O)N(R^7)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)-R^5$, $-C(O)N(R^7)-L^2-O-R^5$, $-C(O)N(R^7)-L^2-S-R^5$, $-C(O)N(R^7)-L^2-C(O)O-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-N(R^7)-R^5$, $-C(O)O-L^2-N(R^7)C(O)O-R^5$, $-C(O)N(R^8)-L^2-N(R^7)C(O)O-R^5$, $-C(O)O-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-O-R^5$ or $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-S-R^5$;

$-Z-$ is a divalent $-C(O)-$, $-C(O)O-$, or $-C(O)N(R^7)-$;

$-L^4-R^5$ is $-(C1-C10 \text{ alkylene})-N(R^7)-R^5$, $-(C1-C10 \text{ alkylene})-O-R^5$, $-(C1-C10 \text{ alkylene})-S-R^5$, $-(C2-C10 \text{ alkenylene})-N(R^7)-R^5$, $-(C2-C10 \text{ alkenylene})-O-R^5$ or $-(C2-C10 \text{ alkenylene})-S-R^5$;

R^7 , R^8 and R^9 each is independently $-H$, $C1-C10$ alkyl, or $C2-C10$ alkenyl;

L^2 and L^3 each is intendedly divalent $-(C1-C10 \text{ alkylene})-$, or $-(C2-C10 \text{ alkenylene})-$; and

X is a halogen atom.

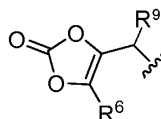
[00048] An adenosine derivative of the present disclosure can be free from a monophosphate group, diphosphate group, tri-phosphate group or a combination thereof. In some embodiments, the R^1 , $R^{1'}$ or R^2 group of an adenosine derivative of the present disclosure is free from a monophosphate group, diphosphate group, tri-phosphate group or a combination thereof. Non-limiting examples of adenosine derivatives having a halogen atom are shown in formulas (1) – (8) and (4-B) (**Fig. 1A – Fig. 1I**).

[00049] In some embodiments, the $C1-C10$ alkyl and $C2-C10$ alkenyl of formula (1) is linear or branched. In some embodiments, the compounds of formula (1) comprise a combination of $C1-C10$ alkyl, $C2-C10$ alkenyl, $C3-C10$ cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl and heteroaryl groups.

[00050] In some embodiments of formula (1), R^1 is H and R^2 is $-C(O)N(R^3)(R^3)$. In some embodiments, R^1 is $-C(O)N(R^3)(R^3)$ and R^2 is H . In some embodiments, R^3

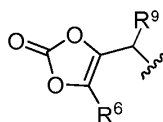
is C1-C5 alkyl or C3-C6 cycloalkyl and $R^{3'}$ is H. In some embodiments, R^3 is methyl, ethyl, or isopropyl and $R^{3'}$ is H.

[00051] In some embodiments of formula (1), R^1 is H and R^2 is $-R^5$ or $-L^1-R^5$. In some embodiments, R^1 is $-L^1-R^5$ and R^2 is H. In some embodiments, $-L^1-R^5$ is $-C(O)N(R^7)-L^2-N(R^7)-R^5$, $-C(O)O-L^2-OR^5$, $-C(O)N(R^7)-L^2-N(R^7)-C(O)O-R^5$, $-C(O)O-L^2-N(R^7)-C(O)O-R^5$, $-C(O)N(R^7)-L^2-N(R^8)-C(O)N(R^8)-R^5$, or $-C(O)O-L^2-N(R^8)-$



$C(O)N(R^8)-R^5$. In some embodiments, R^5 is . In some embodiments, R^6 is C1-C5 alkyl. In some embodiments, R^6 is methyl, ethyl, or isopropyl. In some embodiments, R^6 is methyl. In some embodiments, R^7 is each independently H or Me. In some embodiments, R^9 is H, F, or Me. In some embodiments, R^9 is H. In some embodiments, L^2 is C2-C5 alkylene. In some embodiments, L^2 is ethylene or propylene. In some embodiments, L^2 is ethylene.

[00052] In some embodiments of formula (1), R^1 is $-C(O)O-R^5$ or $-R^5$ and R^2 is H. In some embodiments, R^1 is H and R^2 is $-C(O)O-R^5$ or $-R^5$. In some embodiments,



R^5 is . In some embodiments, R^6 is C1-C5 alkyl. In some embodiments, R^6 is methyl, ethyl, or isopropyl. In some embodiments, R^6 is methyl. In some embodiments, R^9 is H, F, or Me. In some embodiments, R^9 is H.

[00053] In some embodiments of formula (1), R^1 is $-L^1-R^5$. In some embodiments, $R^{1'}$ is $-H$ or $-L^1-R^5$. In some embodiments, $R^{1'}$ is $-H$. In some embodiments, $R^{1'}$ is $-L^1-R^5$. In some embodiments, R^1 is $-L^1-R^5$ and $R^{1'}$ is H. In some embodiments, R^1 is $-L^1-R^5$ and $R^{1'}$ is $-L^1-R^5$. In some embodiments, R^1 is $-L^1-R^5$, $R^{1'}$ is H, and R^2 is H. In some embodiments, R^1 is $-L^1-R^5$, $R^{1'}$ is $-L^1-R^5$, and R^2 is H. In some embodiments, $-L^1-R^5$ is selected from the group consisting of $-(C1-C10 \text{ alkylene})-N(R^7)-R^5$, $-(C1-C10 \text{ alkylene})-O-R^5$, $-C(O)O-L^2-N(R^7)-R^5$, $-C(O)O-L^2-O-R^5$, $-C(O)O-L^2-C(O)O-R^5$, $-C(O)O-L^2-C(O)N(R^7)-R^5$, $-C(O)N(R^7)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)-R^5$, $-C(O)N(R^7)-L^2-O-R^5$, $-C(O)O-L^2-N(R^7)C(O)O-R^5$, $-C(O)N(R^8)-L^2-N(R^7)C(O)O-R^5$, $-$

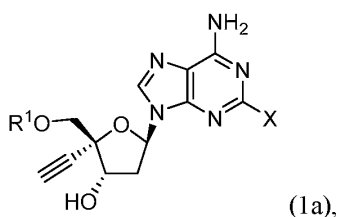
$C(O)O-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)O-R^5$, and $-C(O)N(R^7)-L^2-C(O)N(R^8)-R^5$. In some embodiments, $-L^1-R^5$ is selected from the group consisting of $-C(O)O-R^5$, $-C(O)O-L^2-N(R^7)-R^5$, $-C(O)O-L^2-N(R^7)C(O)O-R^5$, $-C(O)N(R^8)-L^2-N(R^7)C(O)O-R^5$, $-C(O)O-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)-R^5$, and $-C(O)N(R^7)-L^2-C(O)N(R^8)-R^5$. In some embodiments, $-L^1-R^5$ is $-C(O)O-R^5$. In some embodiments, R^2 is H.

[00054] The divalent linker L^1 can also comprise one or more repeats of a same group or a combination of different groups. In some embodiments, the L^1 comprises $-C(O)O-$ and C1-C10 alkyl. In some embodiments, the L^1 comprises two or more repeats of $-C(O)O-$. In some embodiments, the L^1 comprises two or more repeats of $-C(O)O(CH_2)_n-$. In some embodiments, the L^1 comprises two or more repeats of $-C(O)N(R^7)-$. In some embodiments, the L^1 comprises two or more repeats of $-C(O)N(R^7)(CH_2)_n-$. In some embodiments, the L^1 comprises a combination of $-C(O)O-$, C1-C10 alkyl, and $-C(O)N(R^7)-$. In some embodiments, the L^1 comprises a combination of $-C(O)O-$, $-(CH_2)_n-$ and $-C(O)N(R^7)-$. In some embodiments, the L^1 comprises a combination of $-C(O)N(R^7)-$ and C1-C10 alkyl. In some embodiments, the L^1 comprises two or more repeats of $-C(O)O(CH_2)_n-C(O)N(R^7)-$. In some embodiments, n is an integer from 0 to 10. In some embodiments, n is an integer from 1 to 3. As understood in the art, the above combination are non-limiting examples, and other chemically possible combinations of L^1 are also contemplated by the present disclosure.

[00055] An adenosine derivative of this disclosure can comprise one or more isomers thereof. An isomer can comprise a chiral isomer, also known as stereoisomer, that comprises one or more chiral centers, a tautomer that can interconvert via the relocation of a proton or other atom, such as amino isomer, imino isomer, or a combination thereof. In examples, an adenosine derivative can have an amino isomer, an imino isomer or a combination thereof. In further examples, an adenosine derivative can comprise enantiomers, diastereomers and cis/trans isomers, tautomers or a combination thereof. An isomer that can have reverse transcriptase inhibitor (RTI) activity in vivo can be particularly preferred.

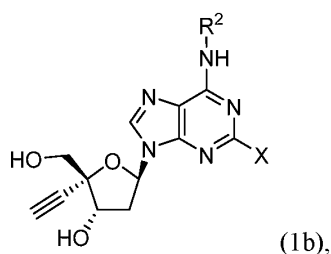
[00056] In some embodiments of formula (1), the X is a halogen atom selected from the group consisting of fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)). In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is Br.

[00057] In some embodiments, the present disclosure is directed to an adenosine derivative or pharmaceutically acceptable salt, tautomer, or solvate thereof having a formula (1a):



wherein R¹ and X are as defined above for formula (1).

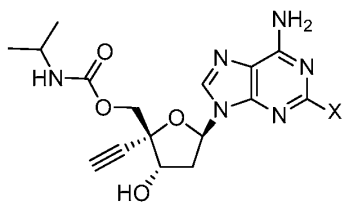
[00058] In some embodiments, the present disclosure is directed to an adenosine derivative or pharmaceutically acceptable salt, tautomer, or solvate thereof having a formula (1b):



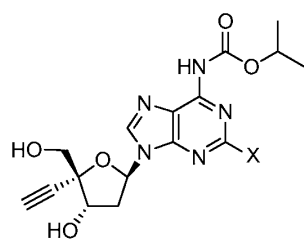
wherein R² and X are as defined above for formula (1).

[00059] In some embodiments, the adenosine derivative of the present disclosure is selected from the group consisting of:

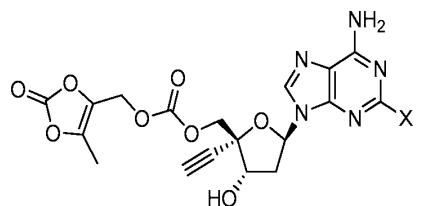
formula (2):



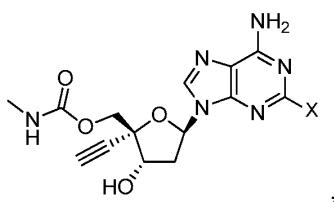
formula (3):



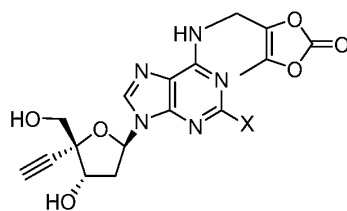
formula (4):



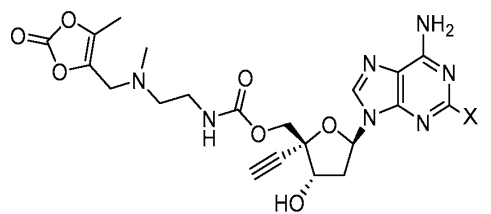
formula (5):



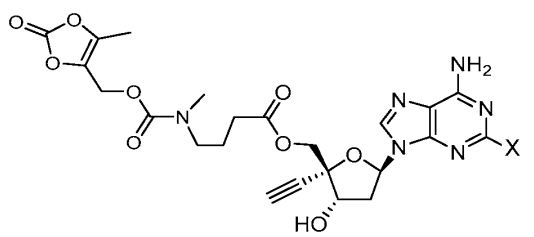
formula (6):



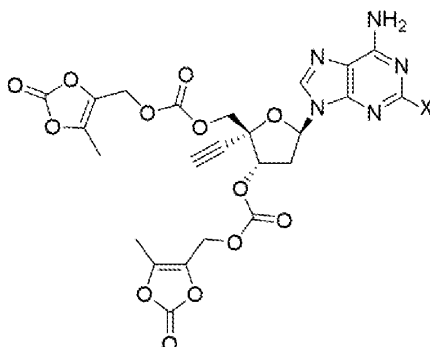
formula (7):



formula (8):



formula (4-B):

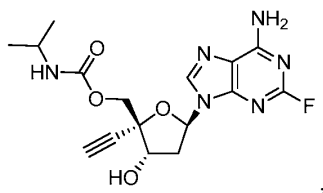


or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

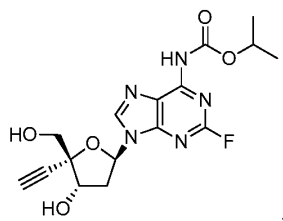
[00060] In some embodiments, X is Cl, F or Br. In some embodiments, X is F.

[00061] In further embodiments, an adenosine derivative of the present disclosure is selected from the group consisting of:

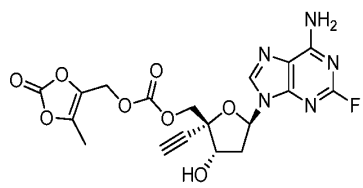
formula (2-A):



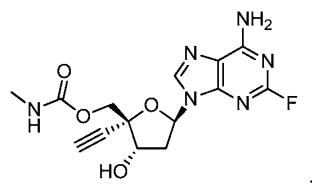
formula (3-A):



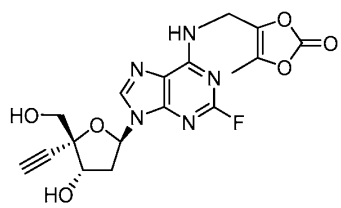
formula (4-A):



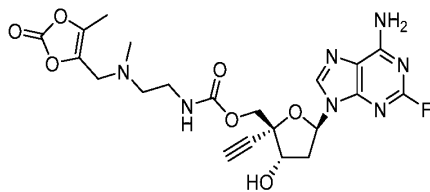
formula (5-A):



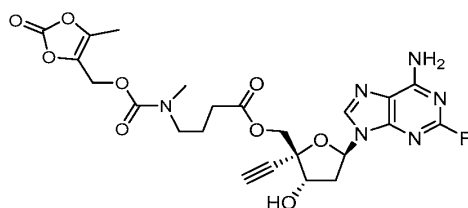
formula (6-A):



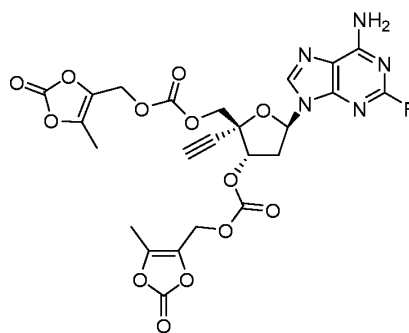
formula (7-A):



formula (8-A):



Formula (4-C):



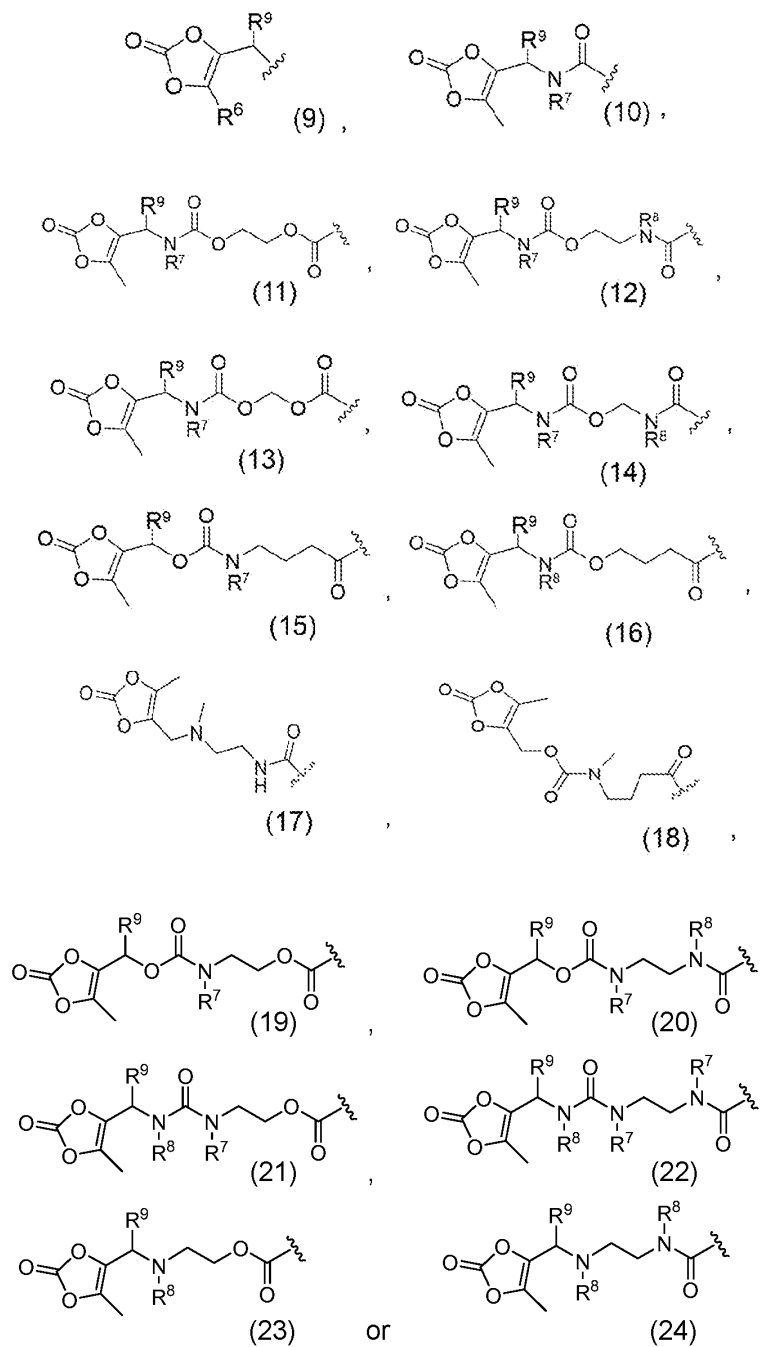
or a stereoisomer, pharmaceutically acceptable salt, tautomer, or solvate thereof (**Fig. 2A-Fig. 2I**).

[00062] In some embodiments, the adenosine compound of the present disclosure is an isomer of formula (1)-(8), formula (1a), formula (1b), or formula (1-A)-(8-A). In some embodiments, the isomer is a stereoisomer, e.g., an enantiomer or a diastereomer. In some embodiments, the isomer is an inhibitor of reverse transcriptase having in vivo activity.

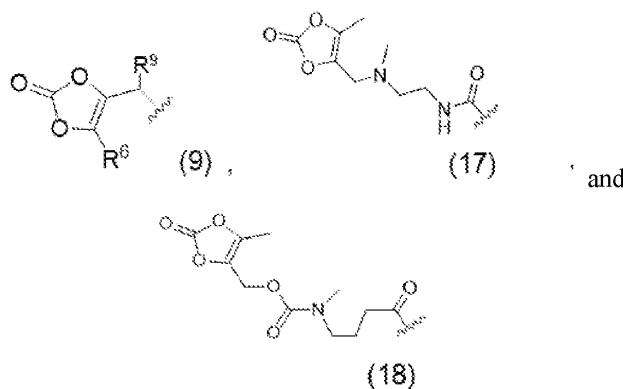
[00063] As disclosed herein, an adenosine derivative of the present disclosure comprises ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate, isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-

yl)carbamate, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate, 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate, [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl)methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate, or a pharmaceutically acceptable salt thereof.

[00064] In some embodiments, the adenosine derivative of the present disclosure comprises R^1 , $R^{1'}$, or R^2 , each independently comprising one or more 5- to 10-membered heterocyclic rings. The R^1 , $R^{1'}$, or R^2 each can independently comprise a 5-member heterocyclic ring in one embodiments, a 6-member heterocyclic ring in another embodiment, or a 6-10-member heterocyclic ring in yet another embodiments. A heterocyclic ring of the present disclosure can have one or more substituents. In some embodiments, a 5-membered heterocyclic ring, comprises carbon atoms and a range of from 1 to 4 heteroatoms selected from the group consisting of N, O, S. In some embodiments, a 5-membered heterocyclic ring comprises from 1 to 3 O atoms. In further embodiments, R^1 , $R^{1'}$, or R^2 each independently comprises a 5-membered heterocyclic ring of formulas 9 – 24. In even further embodiments, an adenosine derivative of the present disclosure comprises R^1 , $R^{1'}$, or R^2 that each independently comprise an aforementioned $-R^5$, $-L^1-R^5$, $-Z-L^4-R^5$ group. In some embodiments, the $-R^5$, $-L^1-R^5$, $-Z-L^4-R^5$ is selected from formulas 9 – 24 (**Fig. 3A-Fig. 3J** and **Fig. 4A-Fig. 4F**):



[00065] In some embodiments, the $-R^5$, $-L^1-R^5$, $-Z-L^4-R^5$ is selected from group consisting of:



[00066] In some embodiments, an adenosine derivative of the present disclosure comprises R^1 and $R^{1'}$ that each is -H, $-C(O)N(R^3)(R^{3'})$ or $-C(O)OR^4$ and R^2 that is $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$ or one of formulas 9 – 24.

[00067] In another embodiment, an adenosine derivative of the present disclosure comprises R^1 and $R^{1'}$ that each is $-C(O)N(R^3)(R^{3'})$ or $-C(O)OR^4$ and R^2 that is -H, $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$ or one of formulas 9 – 24.

[00068] In yet another embodiment, an adenosine derivative of the present disclosure comprises R^2 that is -H, $-C(O)N(R^3)(R^{3'})$ or $-C(O)OR^4$ and R^1 that is $-C(O)N(R^3)(R^{3'})$ or $-C(O)OR^4$ or one of formulas 9 – 24.

[00069] In yet another embodiment, an adenosine derivative of the present disclosure comprises R^2 that is $-C(O)N(R^3)(R^{3'})$ or $-C(O)OR^4$ and R^1 that is -H, $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$ or one of formulas 9 – 24.

[00070] In yet another embodiment, an adenosine derivative of the present disclosure comprises R^1 and $R^{1'}$ that each that is -H, $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$, $-R^5$, $-L^1-R^5$, $-Z-L^4-R^5$ or one of one of formulas 9 – 24 and R^2 that is $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$, $-R^5$, $-L^1-R^5$, $-Z-L^4-R^5$ or one of formulas 9 – 24.

[00071] In yet another embodiment, an adenosine derivative of the present disclosure comprise R^1 that is $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$, $-R^5$, $-L^1-R^5$, $-Z-L^4-R^5$ or one of one of formulas 9 – 24 and R^2 that is -H, $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$, $-R^5$, $-L^1-R^5$, $-Z-L^4-R^5$ or one of formulas 9 – 24.

[00072] In yet further embodiments, each of R^1 , $R^{1'}$ and R^2 is independently selected from one of formulas 9 – 24.

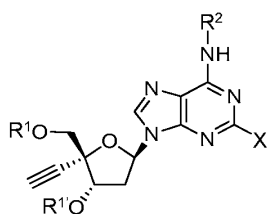
[00073] An adenosine derivative of the present disclosure can undergo conversion to a target drug and can comprise reverse transcriptase inhibitor activity in vivo, reverse transcriptase chain terminator activity in vivo, DNA translocation inhibitor activity in vivo, or a combination thereof.

[00074] An adenosine derivative of the present disclosure can be a prodrug that has no or limited activity in its original form shown herein and can be metabolized in vivo to exhibit the desired activity of a target drug including a reverse transcriptase inhibitor activity, a reverse transcriptase chain terminator activity, DNA translocation inhibitor activity, or a combination thereof.

[00075] Not wishing to be bound by a particular mechanism or theory, Applicants discovered that adenosine derivatives of the present disclosure can be metabolized in vivo to produce a compound or a mixture of compounds similar to or the same as a target drug 4'-ethynyl-2'-fluoro-2'-deoxyadenosine (EFdA) that has reverse transcriptase inhibitor and other antiviral activities.

[00076] As disclosed herein an adenosine derivative of the present disclosure can comprise isomers (e.g., enantiomers, diastereomers, and/or tautomers) thereof, one or more pharmaceutically acceptable salts thereof, one or more solvates including hydrates thereof, solvated salts thereof or a mixture thereof.

[00077] The present disclosure is further directed to a pharmaceutical composition comprising an adenosine derivative disclosed herein and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises an adenosine derivative having a formula (1):

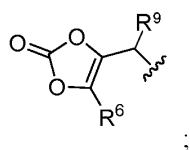


wherein,

R^1 , $R^{1'}$, and R^2 each is independently -H, -C(O)N(R^3)($R^{3'}$), -C(O)OR⁴, -R⁵, -L¹-R⁵, or -Z-L⁴-R⁵, wherein at least one of R^1 and R^2 is not -H;

R^3 , $R^{3'}$ and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

R^5 is:



R^6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

-L¹-R⁵ is -(C1-C10 alkylene)-N(R^7)-R⁵, -(C1-C10 alkylene)-O-R⁵, -(C1-C10 alkyl)-S-R⁵, -(C2-C10 alkenylene)-N(R^7)-R⁵, -(C2-C10 alkenylene)-O-R⁵, -(C2-C10 alkenylene)-S-R⁵, -C(O)O-R⁵, -C(O)O-L²-N(R^7)-R⁵, -C(O)O-L²-O-R⁵, -C(O)O-L²-S-R⁵, -C(O)O-L²-C(O)O-R⁵, -C(O)O-L²-C(O)N(R^7)-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-N(R^7)-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-O-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-S-R⁵, -C(O)N(R^7)-R⁵, -C(O)N(R^7)-L²-N(R^7)-R⁵, -C(O)N(R^7)-L²-O-R⁵, -C(O)N(R^7)-L²-S-R⁵, -C(O)N(R^7)-L²-C(O)O-R⁵, -C(O)N(R^7)-L²-C(O)N(R^8)-R⁵, -C(O)N(R^7)-L²-C(O)N(R^8)-L³-N(R^7)-R⁵, -C(O)O-L²-N(R^7)C(O)O-R⁵, -C(O)N(R^8)-L²-N(R^7)C(O)O-R⁵, -C(O)O-L²-N(R^7)C(O)N(R^8)-R⁵, -C(O)N(R^7)-L²-N(R^7)C(O)N(R^8)-R⁵, -C(O)N(R^7)-L²-C(O)N(R^8)-L³-O-R⁵ or -C(O)N(R^7)-L²-C(O)N(R^8)-L³-S-R⁵;

-Z- is a divalent -C(O)-, -C(O)O-, or -C(O)N(R^7)-;

-L⁴-R⁵ is -(C1-C10 alkylene)-N(R^7)-R⁵, -(C1-C10 alkylene)-O-R⁵, -(C1-C10 alkylene)-S-R⁵, -(C2-C10 alkenylene)-N(R^7)-R⁵, -(C2-C10 alkenylene)-O-R⁵ or -(C2-C10 alkenylene)-S-R⁵;

R^7 , R^8 and R^9 each is independently -H, C1-C10 alkyl, or C2-C10 alkenyl;

L² and L³ each is intendedly divalent -(C1-C10 alkylene)-, or -(C2-C10 alkenylene)-; and

X is a halogen atom.

[00078] As disclosed above, a pharmaceutical composition of the present disclosure comprising an adenosine derivative can be free from monophosphate group, diphosphate group, tri-phosphate group or a combination thereof. In some embodiments, an R¹ and/or R² group of an adenosine derivative of disclosed herein is free from monophosphate group, diphosphate group, tri-phosphate group or a combination thereof.

[00079] In some embodiments, the C1-C10 alkyl and C2-C10 alkenyl is linear or branched. In some embodiments, the adenosine derivative of the pharmaceutical compositions comprises a combination of C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl and heteroaryl.

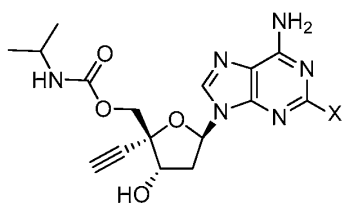
[00080] In some embodiments of the pharmaceutical composition, the adenosine derivative includes a divalent linker L¹ that comprises one or more repeats of a same group or a combination of different groups as disclosed herein. Non-limiting examples of the linker L¹ and other chemically possible combinations include those described above, e.g., in formula (1).

[00081] In some embodiments, an adenosine derivative of the pharmaceutical composition is an isomer of formula (1)-(8), formula (1a), formula (1b), formula (1-A)-(8-A), formula (4-B), or formula (4-C). Isomers described above, such as tautomers, enantiomers, diastereomers, cis/trans isomers or a combination thereof can be suitable. In some embodiments, the isomer is an inhibitor of reverse transcriptase that has in vivo activity.

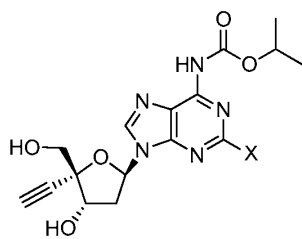
[00082] In some embodiments, the X is a halogen atom selected from the group consisting of fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)). In one embodiment, X is F. In another embodiment, X is Cl. In yet another embodiment, X is Br. Non-limiting examples of adenosine derivatives of the present disclosure are shown in **Fig. 1A-Fig. 1I**.

[00083] In some embodiments, the pharmaceutical composition of the present disclosure comprises an adenosine derivative having a formula selected from the group consisting of:

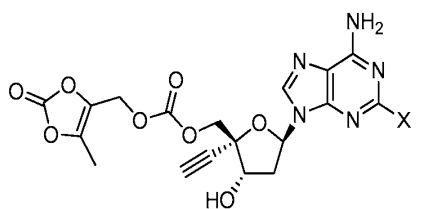
formula (2):



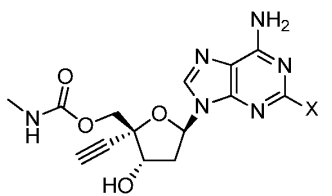
formula (3):



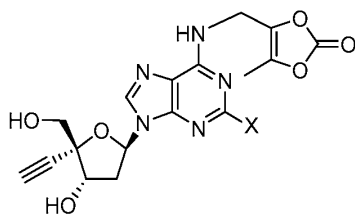
formula (4):



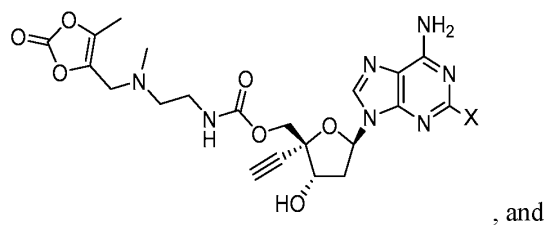
formula (5):



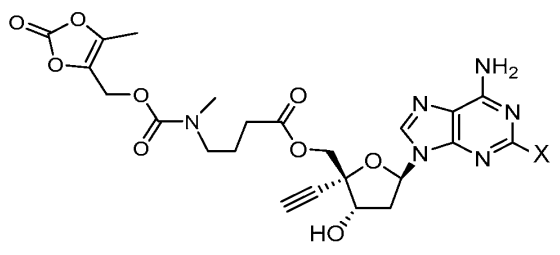
formula (6):



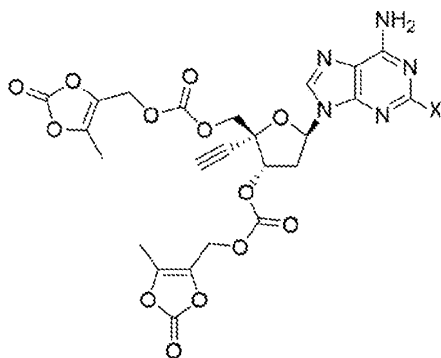
formula (7):



formula (8):



formula (4-B):

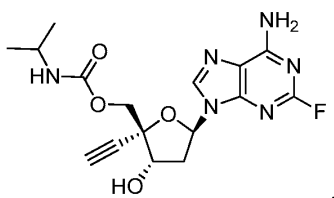


or a pharmaceutically acceptable salt, tautomer, solvate, or a combination thereof.

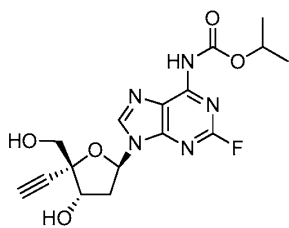
[00084] In some embodiments, X is Cl, F or Br. In some embodiments, X is F.

[00085] In some embodiments, the pharmaceutical composition of the present disclosure comprises an adenosine derivative having a formula selected from the group consisting of:

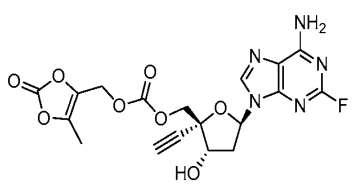
formula (2-A):



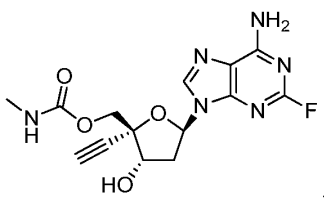
formula (3-A):



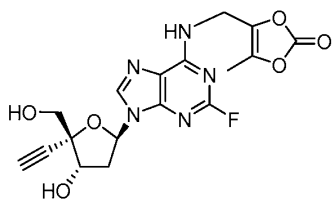
formula (4-A):



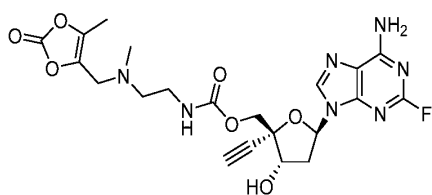
formula (5-A):



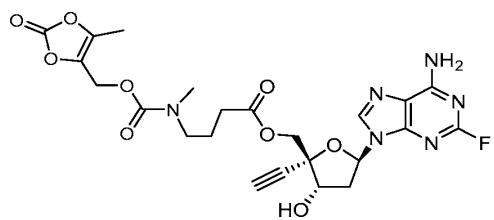
formula (6-A):



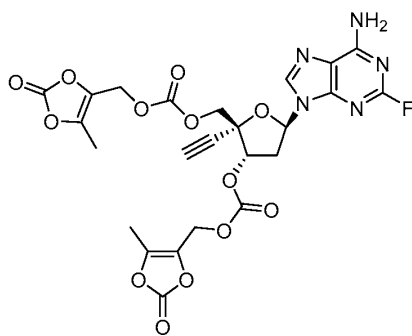
formula (7-A):



formula (8-A):



formula (4-C):

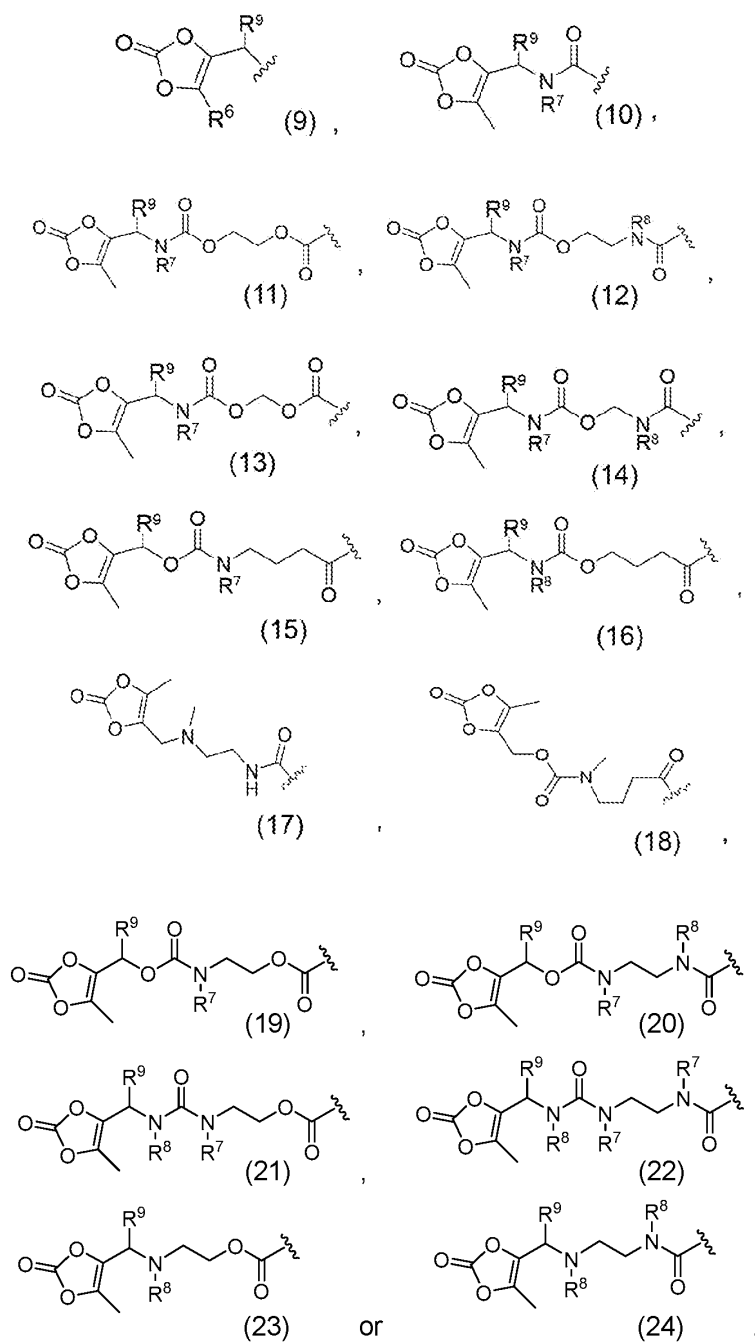


an stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a combination thereof (**Fig. 2A- Fig. 2I**).

[00086] In some embodiments, the adenosine compound of the present disclosure is an isomer of formula (1)-(8), formula (1a), formula (1b), formula (1-A)-(8-A), formula (4-B), or formula (4-C). In some embodiments, the isomer is a stereoisomer, e.g., an enantiomer or a diastereomer. In some embodiments, the isomer is an inhibitor of reverse transcriptase having in vivo activity.

[00087] As disclosed herein, the pharmaceutical composition of the present disclosure comprises an adenosine derivative selected from the group consisting of: ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate, isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate, 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate, [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl)methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate, and any pharmaceutically acceptable salts thereof.

[00088] In some embodiments, the pharmaceutical composition of the present disclosure includes an adenosine derivative comprising an R⁵, -L¹-R⁵ or -Z-L⁴-R⁵ selected from formulas 9 – 24:



[00089] In some embodiments, a pharmaceutical composition of the present disclosure comprises an adenosine derivative that comprises R^1 and $R^{1'}$ that each is -H,

$-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$ or $-\text{C}(\text{O})\text{OR}^4$ and R^2 that is $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$, $-\text{C}(\text{O})\text{OR}^4$ or one of formulas 9 – 24.

[00090] In another embodiment, a pharmaceutical composition of the present disclosure comprises an adenosine derivative that comprises R^1 that is $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$ or $-\text{C}(\text{O})\text{OR}^4$ and R^2 that is $-\text{H}$, $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$, $-\text{C}(\text{O})\text{OR}^4$ or one of formulas 9 – 24.

[00091] In yet another embodiment, a pharmaceutical composition of the present disclosure comprises an adenosine derivative that comprises R^2 that is $-\text{H}$, $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$ or $-\text{C}(\text{O})\text{OR}^4$ and R^1 that is $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$ or $-\text{C}(\text{O})\text{OR}^4$ or one of formulas 9 – 24.

[00092] In yet another embodiment, a pharmaceutical composition of the present disclosure comprises an adenosine derivative that comprises R^2 that is $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$ or $-\text{C}(\text{O})\text{OR}^4$ and R^1 and $\text{R}^{1'}$ that is each $-\text{H}$, $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$, $-\text{C}(\text{O})\text{OR}^4$ or one of formulas 9 – 24.

[00093] In yet another embodiment, a pharmaceutical composition of the present disclosure comprises an adenosine derivative that comprises R^1 and $\text{R}^{1'}$ that is each $-\text{H}$, $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$, $-\text{C}(\text{O})\text{OR}^4$, $-\text{R}^5$, $-\text{L}^1\text{-R}^5$, $-\text{Z-L}^4\text{-R}^5$ or one of one of formulas 9 – 24 and R^2 that is selected from $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$, $-\text{C}(\text{O})\text{OR}^4$, $-\text{R}^5$, $-\text{L}^1\text{-R}^5$, $-\text{Z-L}^4\text{-R}^5$ or one of formulas 9 – 24.

[00094] In yet another embodiment, a pharmaceutical composition of the present disclosure comprises an adenosine derivative that comprises R^1 that is $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$, $-\text{C}(\text{O})\text{OR}^4$, $-\text{R}^5$, $-\text{L}^1\text{-R}^5$, $-\text{Z-L}^4\text{-R}^5$ or one of one of formulas 9 – 24 and R^2 that is selected from $-\text{H}$, $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^{3'})$, $-\text{C}(\text{O})\text{OR}^4$, $-\text{R}^5$, $-\text{L}^1\text{-R}^5$, $-\text{Z-L}^4\text{-R}^5$ or one of formulas 9 – 24.

[00095] In yet further embodiments, a pharmaceutical composition of the present disclosure comprises an adenosine derivative that comprises R^1 , $\text{R}^{1'}$, and R^2 each is independently selected from one of formulas 9 – 24.

[00096] In some embodiments, R^3 , $\text{R}^{3'}$ and R^4 each is independently $-\text{H}$, C1-C10 alkyl, C2-C10 alkenyl, or C3-C10 cycloalkyl. In some embodiments, R^3 , $\text{R}^{3'}$ and R^4 each is independently $-\text{H}$, C1-C5 alkyl, C2-C5 alkenyl, or C3-C6 cycloalkyl. In some embodiments, R^3 , $\text{R}^{3'}$ and R^4 each is independently $-\text{H}$ or C1-C5 alkyl. In some

embodiments, the C1-C5 alkyl is methyl, ethyl, or isopropyl. In some embodiments, R³, R^{3'} and R⁴ each is independently -H, methyl, or isopropyl.

[00097] In some embodiments, R⁶ is -H, C1-C10 alkyl, C2-C10 alkenyl, or C3-C10 cycloalkyl. In some embodiments, R⁶ is -H, C1-C5 alkyl, C2-C5 alkenyl, or C3-C6 cycloalkyl. In some embodiments, R⁶ is -H, C1-C3 alkyl, or C2-C4 alkenyl. In some embodiments, R⁶ is selected from the group consisting of -H, methyl, ethyl, isopropyl, or cyclopropyl. In some embodiments, R⁶ is methyl.

[00098] In some embodiments, R⁷ and R⁸ each is independently -H, C1-C10 alkyl, or C3-C6 cycloalkyl. In some embodiments, R⁷ and R⁸ each is independently -H, C1-C5 alkyl, or C3-C6 cycloalkyl. In some embodiments, R⁷ and R⁸ each is independently -H, methyl, ethyl, isopropyl, or cyclopropyl.

[00099] In some embodiments, R⁹ is -H, F, C1-C10 alkyl, or C2-C10 alkenyl. In some embodiments R⁹ is -H, F, C1-C3 alkyl, or C2-C4 alkenyl. In some embodiments, R⁹ is -H, F, or C1-C3 alkyl. In some embodiments, R⁹ is -H.

[000100] As described, the pharmaceutical composition of the present disclosure comprises a pharmaceutically acceptable carrier.

[000101] Non-limiting examples of a pharmaceutically acceptable carrier include a pharmaceutical excipients surfactant, emulsifier, filler, carrier, isotonicifier, dispersing agent, viscosity modifier, resuspending agent, buffer or a combination thereof. Pharmaceutical excipients typically do not have properties of a medicinal or drug active ingredient, also known as active pharmaceutical ingredient (API) and are typically used to streamline the manufacture process or packaging of the active ingredients, or to deliver an API to a patient or other subject. Pharmaceutical acceptable carrier, excipients or inactive ingredients from the Inactive Ingredients Database available from US FDA (<https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download>) can be suitable. Some of Generally Recognized As Safe (GRAS) food substances available from US FDA's GRAS Substances (SCOGS) Database (<https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database>) can also be suitable.

[000102] In some embodiments of the present disclosure, the pharmaceutical acceptable carrier comprises acacia, animal oils, benzyl alcohol, benzyl benzoate, calcium stearate, carbomers, cetostearyl alcohol, cetyl alcohol, cholesterol, cyclodextrins, dextrose, diethanolamine, emulsifying wax, ethylene glycol palmitostearate, glycerin, glycerin monostearate, glycerol stearate,, glyceryl monooleate, glyceryl monostearate, hydrous, histidine, hydrochloric acid, hydroxypropyl cellulose, hydroxypropyl- β -cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), lanolin, lanolin alcohols, lecithin, medium-chain triglycerides, metallic soaps, methylcellulose, mineral oil, monobasic sodium phosphate, monoethanolamine, oleic acid, polyethylene glycols (PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer (poloxamer), polyoxyethylene alkyl ethers, polyoxyethylene castor oil, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polysorbate, polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), povidone, propylene glycol alginate, saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, sorbitan esters, stearic acid, stearyl alcohol, sunflower oil, tragacanth, triethanolamine, vegetable oils, water, xanthan gum, or combinations thereof.

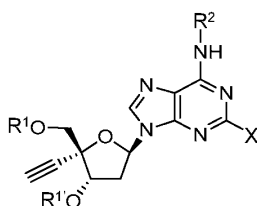
[000103] In further embodiments, the pharmaceutical acceptable carrier comprises dextrose, glycerin, histidine, hydrochloric acid, hydroxypropyl cellulose, hydroxypropyl- β -cyclodextrin (HPBCD), hypromellose (hydroxypropyl methylcellulose (HPMC)), polyoxyethylene (20) sorbitan monolaurate (Tween 20, Polysorbate 20), polyethylene glycols (PEG 400, PEG 3350, PEG 4000, PEG 6000), polyoxyethylene-polyoxypropylene copolymer (Poloxamer 188, Poloxamer 407), polyoxyethylene (20) sorbitan monooleate (Tween 80, Polysorbate 80), saline, sodium chloride, sodium citrate, sodium citrate dihydrate, sodium lauryl sulfate, sodium phosphate monobasic, sodium phosphate dibasic, or a combination thereof.

[000104] The pharmaceutical composition of the present disclosure can further comprise an effective dosage of one or more anti-HIV agents (also referred to as anti-HIV agent) selected from abacavir, abacavir sulfate, lamivudine, amprenavir,

atazanavir, atazanavir sulfate, AZT, bictagrevir, cabotegravir, darunavir, dideoxycytidine, dideoxyinosine, dolutegravir, doravirine, efavirenz, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, 4'-ethynyl-2'-fluoro-2'-deoxyadenosine, elvitegravir, etravirine, fosamprenavir calcium, indinavir, indinavir sulfate, lamivudine, lopinavir, a combination of lopinavir and ritonavir, darunavir, a combination of darunavir and cobicistat, maraviroc, nelfinavir, nelfinavir mesylate, nevirapine, PPL-100, raltegravir, rilpivirine, stavudine, tipranavir, vicriviroc or a combination thereof.

[000105] In some embodiments, the pharmaceutical composition of the present disclosure comprises an adenosine derivative, e.g., formula (1)-(8), formula (1a), formula (1b), or formula (1-A)-(8-A), and the one or more anti-HIV agents in a single formulation that can be administered to a subject together. The pharmaceutical composition of the present disclosure can comprise the adenosine derivative and the one or more anti-HIV agents in separate formulations that can be administered to a subject simultaneously or sequentially. The pharmaceutical composition of the present disclosure can also be mixed together with one or more anti-HIV agents in separate formulations that can be administered to a subject simultaneously.

[000106] The present disclosure is further directed to a method for the treatment of a disease. The method can comprise administering a subject in need thereof an effective dosage of a pharmaceutical composition comprising an adenosine derivative having a formula (1):

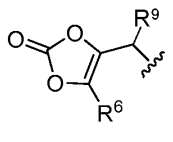


wherein,

R^1 , $R^{1'}$, and R^2 each is independently -H, -C(O)N(R^3)($R^{3'}$), -C(O)OR⁴, -R⁵, -L¹-R⁵, or -Z-L⁴-R⁵, wherein at least one of R^1 and R^2 is not -H;

R^3 , R^3' and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

R^5 is:



R^6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

$-L^1-R^5$ is $-(C1-C10 \text{ alkylene})-N(R^7)-R^5$, $-(C1-C10 \text{ alkylene})-O-R^5$, $-(C1-C10 \text{ alkylene})-S-R^5$, $-(C2-C10 \text{ alkenylene})-N(R^7)-R^5$, $-(C2-C10 \text{ alkenylene})-O-R^5$, $-(C2-C10 \text{ alkenylene})-S-R^5$, $-C(O)O-R^5$, $-C(O)O-L^2-N(R^7)-R^5$, $-C(O)O-L^2-O-R^5$, $-C(O)O-L^2-S-R^5$, $-C(O)O-L^2-C(O)O-R^5$, $-C(O)O-L^2-C(O)N(R^7)-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-N(R^7)-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-O-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-S-R^5$, $-C(O)N(R^7)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)-R^5$, $-C(O)N(R^7)-L^2-O-R^5$, $-C(O)N(R^7)-L^2-S-R^5$, $-C(O)N(R^7)-L^2-C(O)O-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-N(R^7)-R^5$, $-C(O)O-L^2-N(R^7)C(O)O-R^5$, $-C(O)N(R^8)-L^2-N(R^7)C(O)O-R^5$, $-C(O)O-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-O-R^5$ or $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-S-R^5$;

$-Z-$ is a divalent $-C(O)-$, $-C(O)O-$, or $-C(O)N(R^7)-$;

$-L^4-R^5$ is $-(C1-C10 \text{ alkylene})-N(R^7)-R^5$, $-(C1-C10 \text{ alkylene})-O-R^5$, $-(C1-C10 \text{ alkylene})-S-R^5$, $-(C2-C10 \text{ alkenylene})-N(R^7)-R^5$, $-(C2-C10 \text{ alkenylene})-O-R^5$ or $-(C2-C10 \text{ alkenylene})-S-R^5$;

R^7 , R^8 and R^9 each is independently -H, C1-C10 alkyl, or C2-C10 alkenyl;

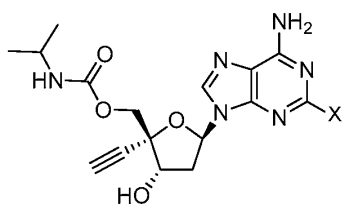
L^2 and L^3 each is intendedly divalent $-(C1-C10 \text{ alkyl})-$, or $-(C2-C10 \text{ alkenyl})-$;
and

X is a halogen atom.

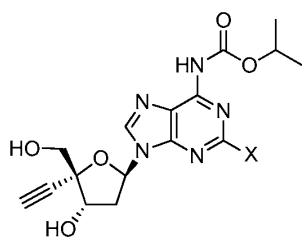
[000107] Any of the aforementioned adenosine derivatives (e.g., formula (1)-(8), formula (1a), formula (1b), or formula (1-A)-(8-A)) or pharmaceutical compositions comprising the adenosine derivatives can be suitable. The X is a halogen atom and can be selected from fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)). In some embodiments, X is F. In another embodiment, X is Cl. In yet another embodiment, X is Br.

[000108] In some embodiments of the present method, the adenosine derivative has a formula selected from the group consisting of:

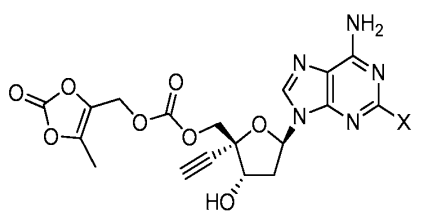
formula (2):



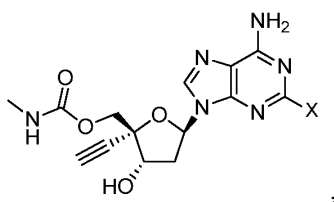
formula (3):



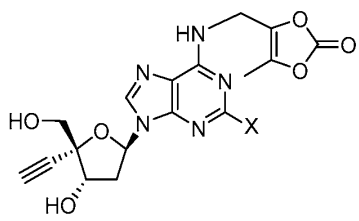
formula (4):



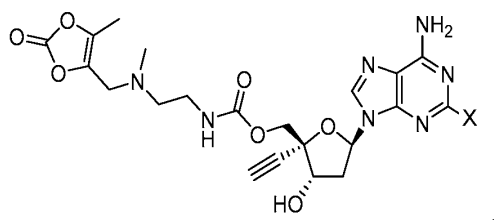
formula (5):



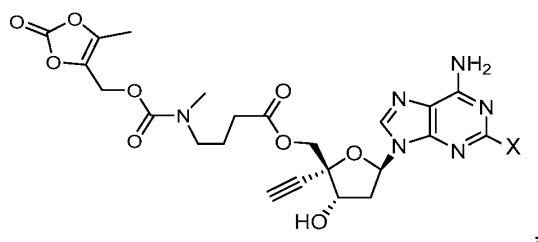
formula (6):



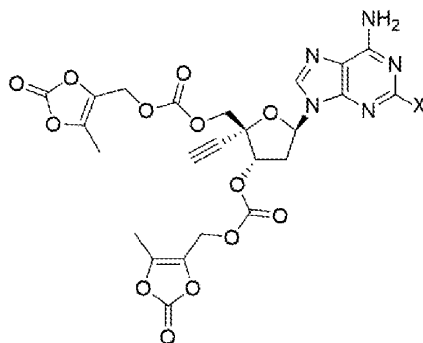
formula (7):



formula (8):



formula (4-B):

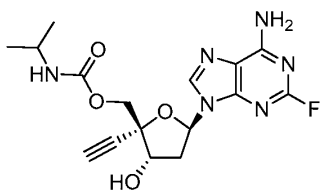


an isomer thereof, or a pharmaceutically acceptable salt thereof.

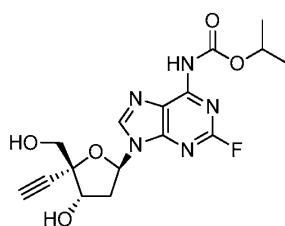
[000109] In some embodiments, X is Cl, F or Br. In some embodiments, X is F.

[000110] In some embodiments of the present method, the adenosine derivative has a formula selected from the group consisting of:

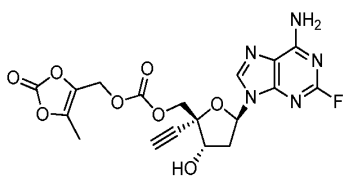
formula (2-A):



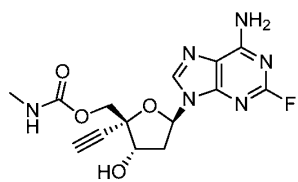
formula (3-A):



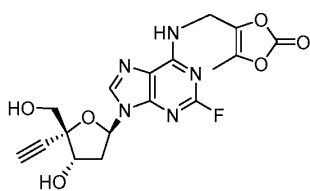
formula (4-A):



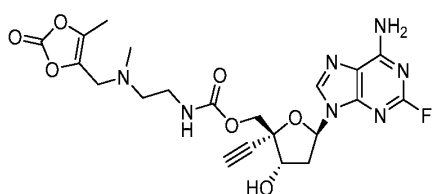
formula (5-A):



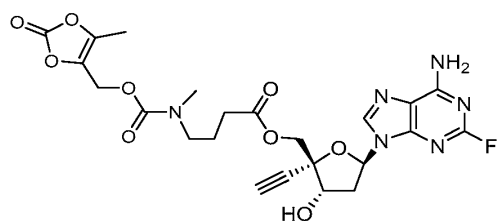
formula (6-A):



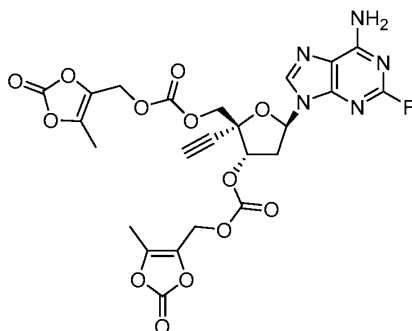
formula (7-A):



formula (8-A):



formula (4-C):

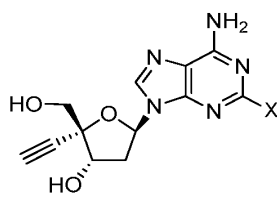


an isomer thereof, or a pharmaceutically acceptable salt thereof.

[000111] As disclosed herein, the present method includes administering a pharmaceutical composition comprising an adenosine derivative, wherein the adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate, isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate, ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate, 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one, or any pharmaceutically acceptable salt thereof.

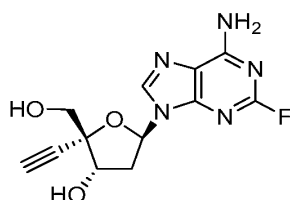
[000112] In the method of the present disclosure, the pharmaceutical composition is administered to a subject via intramuscular (IM) injection, subcutaneous (SC) injection, intravenous (IV) injection, oral administration, topical application, implant application or a combination thereof. An implant application can include an implantable device or a film that contains the pharmaceutical composition disclosed herein. The implant application can comprise vaginal ring, film, membrane, patch, other devices, or a combination thereof.

[000113] The method of the present disclosure can further comprise measuring a specimen of the subject to determine a measured level of a target drug in the specimen, wherein the target drug can have a formula (T-1):



an isomer thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, X is a halogen selected from the group consisting of F, Cl, Br and I. In some embodiments X is I.

[000114] In some embodiments, the target drug can have a formula (T-1A):



an isomer thereof, or a pharmaceutically acceptable salt thereof (**Fig. 5A – Fig. 5B**).

[000115] In some embodiments, the target drug can be (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (also referred to as 4'-ethynyl-2-fluoro-2'-deoxyadenosine, EFdA), or a pharmaceutically acceptable salt thereof.

[000116] In some embodiments, the target drug can be a degradation or metabolized product of the compound (T-1), (T-1A) or EFdA.

[000117] The specimen can be a blood sample, a urine sample, a body fluid sample, a tissue sample or a combination thereof from the subject, such as a patient.

[000118] The measured level of the target drug can be determined with analytical method known to those skilled in the art, such as, but not limited to, HPLC, GC, MS, GC-MS, or a combination thereof.

[000119] The method of the present disclosure can further comprise adjusting the effective dosage to produce a modified effective dosage if the measured level of the

target drug is different from a predetermined target level of the target drug and administering the modified effective dosage to the subject.

[000120] In some embodiments of the present method, the disease is Acquired Immune Deficiency Syndrome (AIDS), wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, multidrug resistant HIV, or an RNA virus infection.

[000121] In some embodiments, the method of the present disclosure further comprises administering to a subject an effective dosage of one or more anti-HIV agents selected from the group consisting of abacavir, abacavir sulfate, lamivudine, amprenavir, atazanavir, atazanavir sulfate, AZT, bictagrevir, cabotegravir, darunavir, dideoxycytidine, dideoxyinosine, dolutegravir, doravirine, efavirenz, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, 4'-ethynyl-2'-fluoro-2'-deoxyadenosine, elvitegravir, etravirine, fosamprenavir calcium, indinavir, indinavir sulfate, lamivudine, lopinavir, a combination of lopinavir and ritonavir, darunavir, a combination of darunavir and cobicistat, maraviroc, nelfinavir, nelfinavir mesylate, nevirapine, PPL-100, raltegravir, rilpivirine, stavudine, tipranavir, and vicriviroc or a combination thereof. Other anti-HIV agents identified or developed, or combination thereof, can also be suitable.

[000122] Combinations of the adenosine derivative of the present disclosure (e.g., formula (1)-(8), formula (1a), formula (1b), or formula (1-A)-(8-A)) and the one or more anti-HIV agents described herein can be useful for the treatment or prophylaxis of AIDS or other HIV related symptoms. The anti-HIV agents can be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, Thomson PDR, Thomson PDR, 57th edition (2003), the 58th edition (2004), or the 59th edition (2005) and the current Physicians' Desk Reference (68th ed.). (2014), Montvale, N.J.: PDR Network.

[000123] An adenosine derivative of the present disclosure and the one or more anti-HIV agents described herein can be administered to a subject together or separately via oral administration, parenteral administration or a combination thereof. The

adenosine derivative and the one or more anti-HIV agents can be administered to the subject with a daily, weekly, biweekly or monthly administration schedule.

[000124] The present disclosure is further directed to a use of the pharmaceutical composition for the treatment of a disease in a subject in need thereof, wherein the disease is Acquired Immune Deficiency Syndrome (AIDS), wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, multidrug resistant HIV, or an RNA virus infection. Any of the aforementioned pharmaceutical compositions can be suitable. The pharmaceutical composition can be used together with one or more anti-HIV agents for the treatment of the disease mentioned herein. The adenosine derivative and the one or more anti-HIV agents can be administered to a subject together or separately via oral administration, parenteral administration or a combination thereof. The adenosine derivative and the one or more anti-HIV agents can be administered to the subject with a daily, weekly, biweekly or monthly administration schedule.

[000125] The present disclosure is further directed to a use of the adenosine derivative, optionally, one or more pharmaceutically acceptable carriers, disclosed herein for manufacturing a medicament for treating a disease, wherein the disease is Acquired Immune Deficiency Syndrome (AIDS), wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, multidrug resistant HIV, or an RNA virus infection. Aforementioned adenosine derivatives can be suitable. Aforementioned pharmaceutically acceptable carriers can be suitable.

[000126] The present disclosure is further directed to a method for the prevention of infection in a subject in need thereof, the method comprising administering the subject an effective dosage of a pharmaceutical composition of the present method disclosed herein, wherein the subject is free from detectable symptoms of the infection. In some embodiments, the infection comprises a disease selected from Acquired Immune Deficiency Syndrome (AIDS), an infection of wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, multidrug resistant HIV, an RNA virus infection, or a combination thereof.

[000127] The detectable symptoms include, but are not limited to, symptoms of Acquired Immune Deficiency Syndrome (AIDS), symptoms of infection of HIV viruses

comprising wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, multidrug resistant HIV, or a combination thereof. The detection of the HIV viruses can be done by PCR, reverse PCR, immunodetection of an antigen or an antibody related to AIDS or HIV.

[000128] In some embodiments, the pharmaceutical composition of the present method is administered to said subject with a daily, weekly, biweekly or monthly administration schedule.

[000129] In some embodiments, the method of the present disclosure further comprises administering the subject an effective dosage of one or more anti-HIV agents selected from abacavir, abacavir sulfate, lamivudine, amprenavir, atazanavir, atazanavir sulfate, AZT, bictagrevir, cabotegravir, darunavir, dideoxycytidine, dideoxyinosine, dolutegravir, doravirine, efavirenz, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, 4'-ethynyl-2'-fluoro-2'-deoxyadenosine, elvitegravir, etravirine, fosamprenavir calcium, indinavir, indinavir sulfate, lamivudine, lopinavir, a combination of lopinavir and ritonavir, darunavir, a combination of darunavir and cobicistat, maraviroc, nelfinavir, nelfinavir mesylate, nevirapine, PPL-100, raltegravir, rilpivirine, stavudine, tipranavir, vicriviroc or a combination thereof. The one or more anti-HIV agents can be administered to the subject together with the pharmaceutical composition of this disclosure or separately.

[000130] Without being bound by any particular theory, an advantage of the adenosine derivatives disclosed herein (e.g., formula (1)-(8), formula (1a), formula (1b), formula (1-A)-(8-A), formula (4-B), or formula (4-C)) is the fast conversion to the target drug. As described below, greater than about 60% of the adenosine derivatives of the present disclosure surprisingly and unexpectedly can be converted to the target drug within about 30 min in contact with human plasma.

[000131] The instant disclosure now will be exemplified in the following non-limiting examples.

EXAMPLES

[000132] The present invention is further defined in the following Examples. It should be understood that these Examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these Examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.

Properties of the Adenosine Derivatives

[000133] Properties of the adenosine derivatives are listed in **Table 1**.

Table 1. Nomenclature and properties.

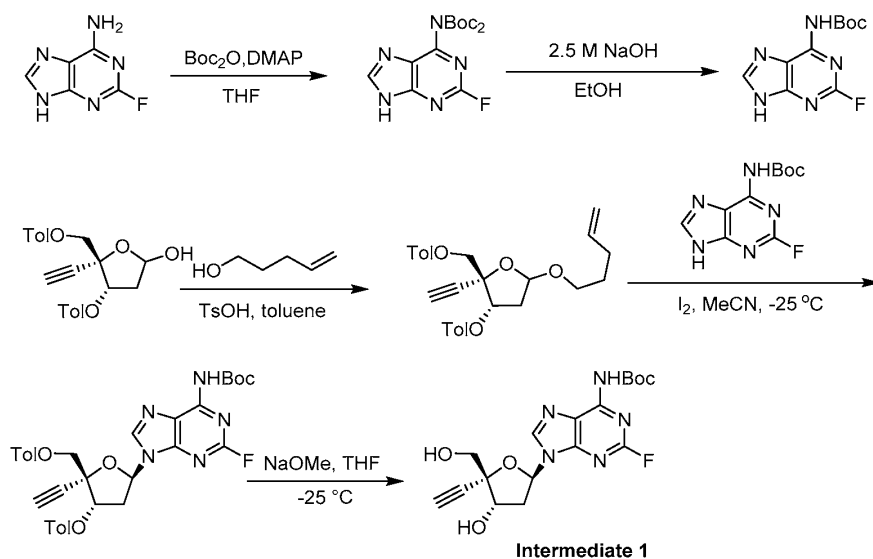
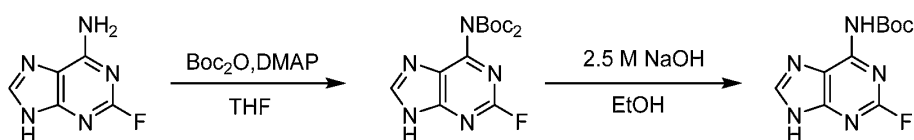
Formula ID	IUPAC Nomenclature	Molecular Weight
T-1A (EFdA)	(2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol	293.25
2-A	((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate	378.36
3-A	isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate	379.34
4-A	((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate	449.35
5-A	((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate	350.31
6-A	4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one	405.34
7-A	((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate	505.46
8-A	((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl 4-(methyl(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)butanoate	548.48
4-C	((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)oxy)tetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate	605.44

Synthesis of Adenosine Derivative Prodrugs:

[000134] Preparation methods, intermediates and synthesis schedules are outlined below.

Intermediate 1:

tert-butyl N-[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate

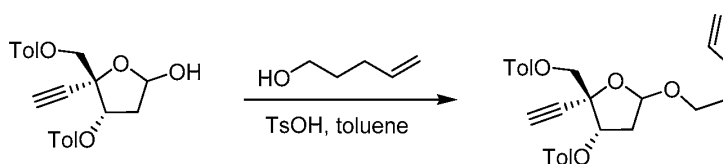
**[000135] Preparation of tert-butyl N-(2-fluoro-9H-purin-6-yl)carbamate**

[000136] To a stirred suspension of 2-fluoro-9H-purin-6-amine (5 g, 32.65 mmol, 1 *eq*) and DMAP (399 mg, 3.27 mmol, 0.1 *eq*) in THF (50 mL) at 0 °C was added (Boc)₂O (24.94 g, 114.29 mmol, 26.3 mL, 3.5 *eq*) in THF (25 mL). The resulting suspension was stirred at 10 °C for 16 h, diluted with MTBE (100 mL) and quenched with water (100 mL). The organic layer was separated, washed with aqueous citric acid (10 wt%, 100 mL), water (2x100 mL) and saturated aqueous sodium chloride (100 mL). The organic layer was concentrated under reduced pressure to give *tert*-butyl N-*tert*-

butoxycarbonyl-N-(2-fluoro-9H-purin-6-yl)carbamate (11.5 g, crude) as a yellow oil, which was used for next reaction without further purification.

[000137] To a mixture of *tert*-butyl *N*-*tert*-butoxycarbonyl-N-(2-fluoro-9H-purin-6-yl)carbamate (11.5 g, 32.55 mmol, 1 *eq*) in EtOH (100 mL) at 20 °C was added NaOH (2.5 M, 78.1 mL, 6 *eq*) over 30 min and the resulting mixture was stirred for 48 h at 20 °C. LCMS showed one main peak with desired *m/z* was detected. The mixture was worked up and solvents were distilled under reduced pressure, the aqueous solution was cooled to 0 °C and neutralized with hydrochloric acid (1 M, 150 mL) to give the slurry. The solid was collected by filtration and dissolved in EtOAc (200 mL), washed with water (2x150 mL) and saturated aqueous sodium chloride (150 mL). The resulting solution was concentrated under reduced pressure to give *tert*-butyl *N*-(2-fluoro-9H-purin-6-yl)carbamate (4 g, 15.80 mmol, 48.5% yield) as a white solid. The crude product was used for the next reaction without further purification. LCMS (ESI) *m/z*, C₁₀H₁₂FN₅O₂: calculated 253.1, found (M+H)⁺: 253.9; (M+Na)⁺: 275.9.

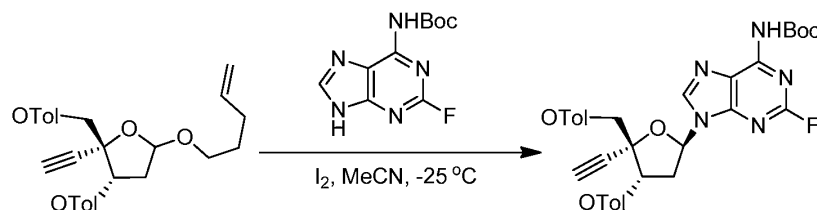
[000138] Preparation of [(2R,3S)-2-ethynyl-3-(4-methylbenzoyl)oxy-5-pent-4-enoxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000139] To a stirred solution of 4-methylbenzenesulfonic acid hydrate (964 mg, 5.07 mmol, 1 *eq*) and pent-4-en-1-ol (480 mg, 5.58 mmol, 1.1 *eq*) in toluene (28 mL) at 0 °C was added a solution of [(2R,3S)-2-ethynyl-5-hydroxy-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (2 g, 5.07 mmol, 1 *eq*) in toluene (32 mL). The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (100 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL) and saturated aqueous sodium chloride (100 mL). The organic layer was concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~8% ethyl acetate/petroleum ether gradient @ 40 mL/min) to give [(2R,3S)-2-ethynyl-3-(4-methylbenzoyl)oxy-5-pent-4-

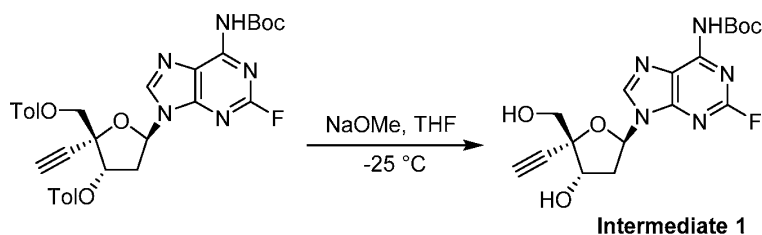
enoxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (1.38 g, 58.2% yield) as colorless oil. LCMS (ESI) m/z , $C_{28}H_{30}O_6$: calculated 462.2, found $(M+Na)^+$: 485.1

[000140] Preparation of [(2R,3S,5R)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxytetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000141] A mixture of [(2R,3S)-2-ethynyl-3-(4-methylbenzoyl)oxy-5-pent-4-enoxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (200 mg, 0.43 mmol, 1 *eq*), tert-butyl *N*-(2-fluoro-9*H*-purin-6-yl)carbamate (131 mg, 0.52 mmol, 1.2 *eq*) and 4 Å MS (1 g, 0.32 mmol) in MeCN (4 mL) was cooled to -25 °C. I_2 (351 mg, 1.38 mmol, 3.2 *eq*) was added and the resulting mixture was stirred for 16 h under a nitrogen atmosphere at -25 °C. The reaction mixture was then warmed to 0 °C and stirred at 0 °C for 2 h. The reaction was quenched with aqueous sodium sulfite (10 mL), diluted with water (10 mL), and then extracted with MTBE (30 mL). The resulting organic layers were washed with aqueous sodium bicarbonate (10 mL) and then with aqueous sodium chloride (10 mL). The organic layer was then concentrated under reduced pressure and purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ether gradient @ 20 mL/min) to give [(2R,3S,5R)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxytetrahydrofuran-2-yl]methyl 4-methylbenzoate (155 mg, 50.0% yield) as a white solid. LCMS (ESI) m/z , $C_{35}H_{32}FN_5O_7$: calculated 629.2, found $(M+H)^+$: 630.1

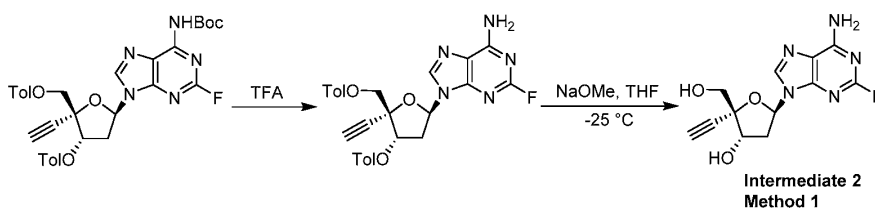
[000142] Preparation of tert-butyl *N*-[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate



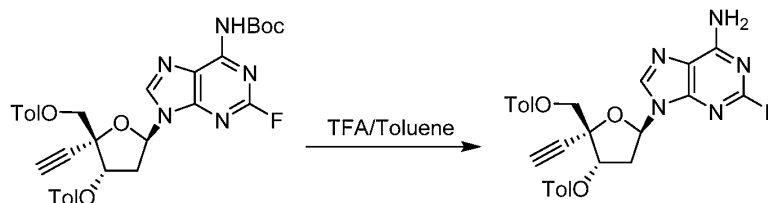
[000143] To a mixture of [(2*R*,3*S*,5*R*)-5-[6-(tert-butoxycarbonylamino)-2-fluoropurin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxytetrahydrofuran-2-yl]methyl 4-methylbenzoate (155 mg, 0.246 mmol, 1 *eq*) in THF (1 mL) at -25 °C was added NaOMe (133 mg, 0.739 mmol, 30%, 3 *eq*) in MeOH (0.5 mL) and the resulting mixture was stirred for 6 h at -25 °C. The mixture was then neutralized with AcOH (0.2 mL) and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~5% MeOH/DCM gradient @ 30 mL/min) to give tert-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate (82 mg, 85.4% yield) as a white solid. LCMS (ESI) *m/z*, C₁₇H₂₀FN₅O₅: calculated 393.1, found (M+Na)⁺: 416.2.

Intermediate 2 (Method 1):

(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol

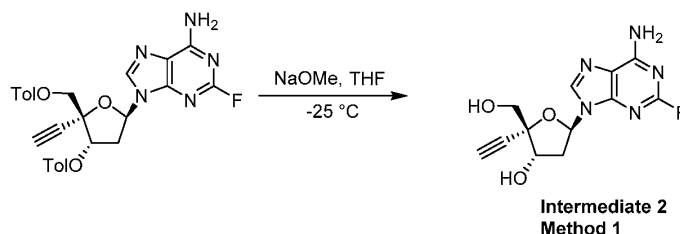


[000144] Preparation of [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000145] To a solution of (2R,3S,5R)-5-(6-((tert-butoxycarbonyl)amino)-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate (220 mg, 0.35 mmol, 1 *eq*) in toluene (2.5 mL) was added TFA (0.25 mL) at 10 °C. The mixture was stirred at 10 °C for 48 h. The mixture was quenched by the addition of saturated sodium hydrogen carbonate (10 mL) and extracted with EtOAc (2 x 10 mL). The organic layer was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ether gradient @ 20 mL/min) to give (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate (130 mg, 70% yield) as a white solid. LCMS (ESI) *m/z* for C₂₈H₂₄FN₅O₅: calculated 529.5, found (M+Na)⁺: 552.1.

[000146] Preparation of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol

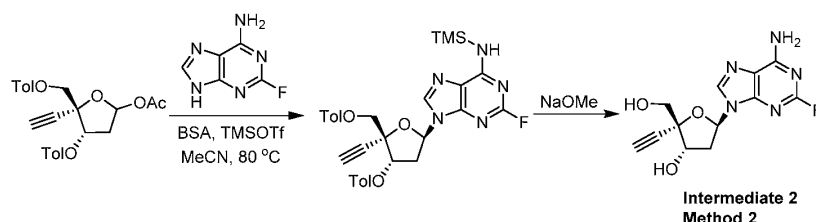


[000147] The mixture of (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate (130 mg, 0.246 mmol, 1 *eq*) in THF (1 mL) was cooled to -25 °C. Then NaOMe (133 mg, 0.737 mmol, 30% purity, 3 *eq*) in MeOH (0.5 mL) was added and the mixture was stirred for 3 h at -25 °C. The mixture was neutralized with AcOH (0.2 mL) and the mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~8%

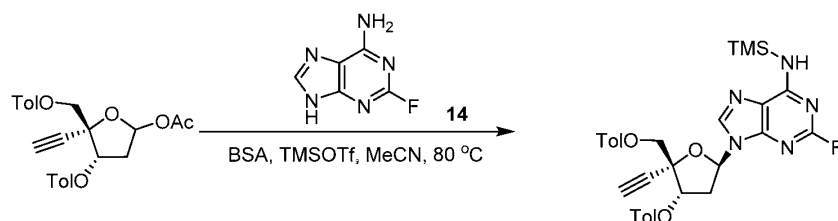
MeOH/DCM gradient @ 20 mL/min) to give (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (46 mg, 64% yield) as a white solid. LCMS (ESI) m/z for $C_{12}H_{12}FN_5O_3$: calculated 293.2, found $(M+H)^+$: 294.1. 1H NMR (DMSO- d_6 , 400MHz) δ (ppm) 8.30 (s, 1H), 7.89 (br s, 2H), 6.24 (dd, $J = 7.2, 5.2$ Hz, 1H), 5.58 (d, $J = 5.6$ Hz, 1H), 5.30 (t, $J = 6.4$ Hz, 1H), 4.52-4.61 (m, 1H), 3.62-3.68 (m, 1H), 3.55 (dd, $J = 12.0, 6.8$ Hz, 1H), 3.52 (s, 1H), 2.64-2.75 (m, 1H), 2.37-2.47 (m, 1H). ^{19}F NMR (DMSO- d_6 , 376MHz) δ (ppm) -51.98 (br s, 1F).

Intermediate 2 (Method 2):

(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol



[000148] Preparation of (2R,3S,5R)-2-ethynyl-5-(2-fluoro-6-((trimethylsilyl)amino)-9H-purin-9-yl)-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate

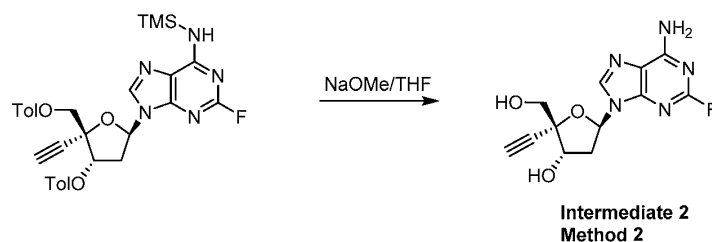


[000149] The CaH_2 was added to acetonitrile and refluxed for 2h, then steamed out under the protection of nitrogen to give anhydrous CH_3CN .

[000150] To a solution of 2-fluoro-9H-purin-6-amine (4.39 g, 28.64 mmol, 1.25 *eq*) in anhydrous CH_3CN (60 mL) was added BSA (13.98 g, 68.74 mmol, 16.99 mL, 3 *eq*) under N_2 . The mixture was stirred at 80 °C for 1 h. After the reaction mixture was cooled to 25 °C, the TMSOTf (6.11 g, 27.49 mmol, 4.97 mL, 1.2 *eq*) was added and the reaction mixture was stirred at 25 °C for 1 h, then [(2R,3S)-5-acetoxy-2-ethynyl-3-

(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (10 g, 22.91 mmol, 1 eq) in anhydrous CH₃CN (60 mL) was added over 1 h at 80 °C and the mixture was stirred at 80 °C for 16 h under N₂. Cooled the reaction mixture to room temperature (15 °C) and still standing for 24 h. The slurry was filtered and washed with cold anhydrous MeCN (10 mL), the mixture was dried under vacuum to give [(2*R*,3*S*,5*R*)-2-ethynyl-5-[2-fluoro-6-(trimethylsilylamino)purin-9-yl]-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (6.58 g, 47.7% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.02 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.86 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.51 (t, *J* = 12 Hz, 1H), 6.05 (m, 1H), 4.82 (d, *J* = 20 Hz, 1H), 4.67 (d, *J* = 20 Hz, 1H), 3.23-3.19 (m, 1H), 2.90-2.85 (m, 1H), 2.68 (s, 1H), 2.43 (d, *J* = 16 Hz, 6H), 0.49 - 0.29 (m, 9H). ¹⁹F NMR (376MHz, CDCl₃) δ (ppm) -49.34 (s, 1F).

[000151] Preparation of (2*R*, 3*S*, 5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl) tetrahydrofuran-3-ol

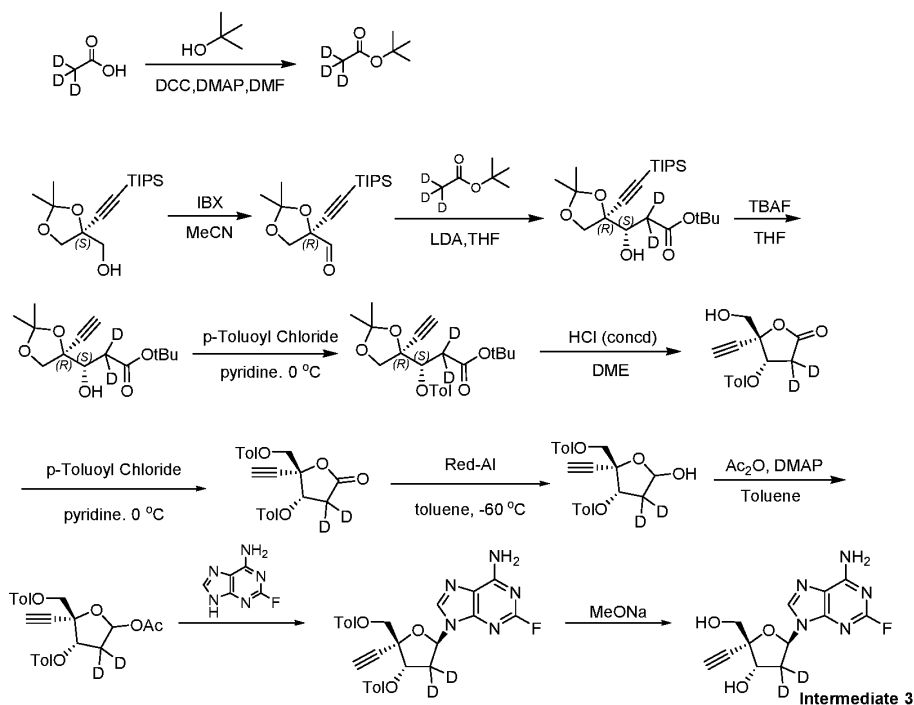


[000152] To a solution of [(2*R*,3*S*,5*R*)-2-ethynyl-5-[2-fluoro-6-(trimethylsilylamino)purin-9-yl]-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (15.5 g, 25.76 mmol, 1 eq) in THF (150 mL) was added NaOMe (6.96 g, 38.64 mmol, 30% purity, 1.5 eq) slowly at -25 °C, the reaction mixture was stirred at -25 °C for 16 h. The mixture was neutralized with AcOH (0.5 mL) to pH ~7 and the mixture was concentrated. The crude product was triturated with CH₃CN:H₂O = 7:3 (100 mL) at 5 °C for 16 h to give (2*R*, 3*S*, 5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl) tetrahydrofuran-3-ol (6.76 g, 89%) as a white solid. LCMS (ESI) *m/z* for C₁₂H₁₂FN₅O₃: calculated 293.2, found (M+H)⁺: 294.1. ¹H NMR (400 MHz, CD₃CN) δ (ppm) 7.99 (s, 1H), 6.35 (br s, 2H), 6.29 (t, *J* = 12 Hz, 1H), 4.65 (t, *J* = 5.6 Hz, 1H), 4.41 (br s, 1H), 3.81-3.78 (m, 1H), 3.71-3.68 (m,

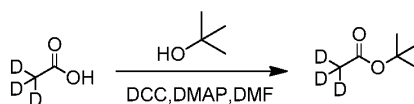
1H), 3.55 (br s, 1H), 2.93 (s, 1H), 2.82-2.77 (m, 1H), 2.49-2.45 (m, 1H). ^{19}F NMR (376 MHz, CD_3CN) δ (ppm) -53.4 (s, 1F).

Intermediate 3:

(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol

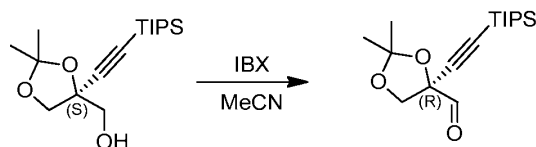


[000153] Preparation of tert-butyl 2,2,2-trideuterioacetate



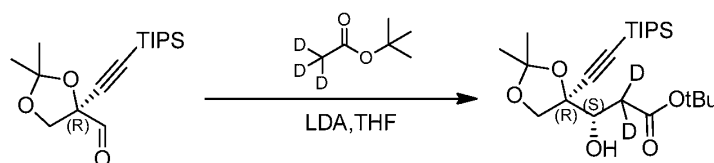
[000154] To a mixture of 2-methylpropan-2-ol (40 g, 539.66 mmol, 51.61 mL, 1 eq) and deuterio 2,2,2-trideuterioacetate (51.87 g, 809.49 mmol, 1.5 eq) in DMF (700 mL) was added DCC (167.02 g, 809.49 mmol, 1.5 eq) and DMAP (13.19 g, 107.93 mmol, 0.2 eq), the mixture was stirred at 25 °C for 64 h. The reaction mixture was distilled in vacuum (105 °C, 0.1 MPa) to give tert-butyl 2,2,2-trideuterioacetate (25.3 g, 39.3% yield) as a colorless liquid. ^1H NMR (400MHz, CDCl_3) δ (ppm) 1.45 (s, 9H).

[000155] Preparation of (4R)-2,2-dimethyl-4-(2-triisopropylsilylethynyl)-1,3-dioxolane-4-carbaldehyde



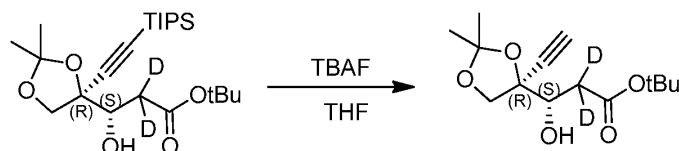
[000156] To a solution of [(4S)-2,2-dimethyl-4-(2-triisopropylsilylethynyl)-1,3-dioxolan-4-yl]methanol (40.2 g, 128.63 mmol, 1 eq) in MeCN (220 mL) was added IBX (108.06 g, 385.90 mmol, 3 eq). The mixture was stirred at 85 °C for 2 h. The mixture was filtered and concentrated to give (4R)-2,2-dimethyl-4-(2-triisopropylsilylethynyl)-1,3-dioxolane-4-carbaldehyde (40 g, crude) as a yellow oil.

[000157] Preparation of tert-butyl (3S)-2,2-dideuterio-3-[(4R)-2,2-dimethyl-4-(2-triisopropylsilylethynyl)-1,3-dioxolan-4-yl]-3-hydroxy-propanoate



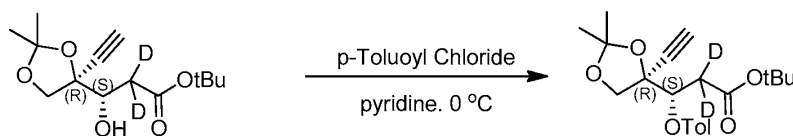
[000158] LDA (2 M in THF, 24.15 mL, 1.5 eq) was added to the solution of THF (45 mL) at -78 °C, tert-butyl 2,2,2-trideuterioacetate (6.14 g, 51.53 mmol, 1.6 eq) was added at -78 °C and the mixture was stirred at -78 °C for 1 h, (4R)-2,2-dimethyl-4-(2-triisopropylsilylethynyl)-1,3-dioxolane-4-carbaldehyde (10 g, 32.21 mmol, 1 eq) in THF (30 mL) was added at -78 °C, then the mixture was stirred at -78 °C for 2 h. D₂O (20 mL) was added, then the mixture was extracted with Ethyl acetate (200 mL x 2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, eluted with 0~70% DCM/ petroleum ether gradient @ 75 mL/min) to give tert-butyl (3S)-2,2-dideuterio-3-[(4R)-2,2-dimethyl-4-(2-triisopropylsilylethynyl)-1,3-dioxolan-4-yl]-3-hydroxy-propanoate (5.17 g, 37.5% yield) as a colorless oil. ¹H NMR (400MHz, CDCl₃) δ(ppm) 4.22 (d, *J* = 8.8Hz, 1H), 4.11 (d, *J* = 8.4Hz, 1H), 4.01 (d, *J* = 4.8Hz, 1H), 2.71 (d, *J* = 5.2Hz, 1H), 1.60 (s, 3H), 1.48 (s, 9H), 1.42 (s, 3H), 1.08 (s, 21H).

[000159] Preparation of tert-butyl (3S)-2,2-dideuterio-3-[(4R)-4-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-propanoate



[000160] To a solution of tert-butyl (3S)-2,2-dideuterio-3-[(4R)-2,2-dimethyl-4-(2-triisopropylsilyl-1-ethynyl)-1,3-dioxolan-4-yl]-3-hydroxy-propanoate (13 g, 30.33 mmol, 1 eq) in THF (130 mL) was added TBAF (1 M in THF, 30.33 mL, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. Ethyl acetate (100 mL) and H₂O (100 mL) was added, then the mixture was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, eluted with 0~15% ethyl acetate/petroleum ether gradient @ 60 mL/min) to give tert-butyl (3S)-2,2-dideuterio-3-[(4R)-4-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-propanoate (6.7 g, 81.1% yield) as a light yellow oil. ¹H NMR (400MHz, CDCl₃) δ(ppm) 4.26 (d, J = 8.8Hz, 1H), 4.16 (d, J = 8.4Hz, 1H), 3.96 (d, J = 4.0Hz, 1H), 3.24–3.20 (m, 1H), 2.55 (s, 1H), 1.62 (s, 3H), 1.50 (s, 9H), 1.42 (s, 3H).

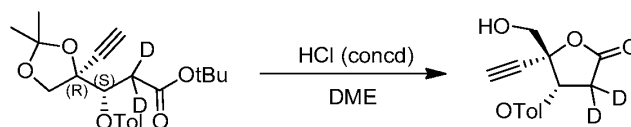
[000161] Preparation of [(1S)-3-tert-butoxy-2,2-dideuterio-1-[(4R)-4-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxo-propyl] 4-methylbenzoate



[000162] To a solution of 4-methylbenzoyl chloride (5.71 g, 36.90 mmol, 4.88 mL, 1.5 eq) in pyridine (60 mL) was added tert-butyl (3S)-2,2-dideuterio-3-[(4R)-4-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-propanoate (6.7 g, 24.60 mmol, 1 eq). The mixture was stirred at 0 °C for 16 h. The ice water (15 mL) was added, then the mixture was stirred at 0 °C for 15 min. The mixture was filtered. The resulting residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash®

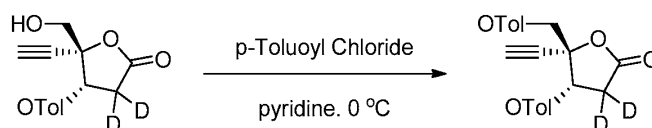
Silica Flash Column, eluted with 0~100% ethyl acetate/petroleum ether gradient @ 60 mL/min) to give [(1S)-3-tert-butoxy-2,2-dideuterio-1-[(4R)-4-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxo-propyl] 4-methylbenzoate (9.2 g, 95.8% yield) as a colorless oil.

[000163] Preparation of [(2R,3S)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)-5-oxo-tetrahydrofuran-3-yl] 4-methylbenzoate



[000164] To a solution of [(1S)-3-tert-butoxy-2,2-dideuterio-1-[(4R)-4-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxo-propyl] 4-methylbenzoate (9.2 g, 23.56 mmol, 1 eq) in DME (90 mL) was added HCl (conc.) (7.16 g, 70.68 mmol, 7.02 mL, 36% purity, 3 eq). The mixture was stirred at 50 °C for 16 h. The mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, eluted with 0~30% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give [(2R,3S)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)-5-oxo-tetrahydrofuran-3-yl] 4-methylbenzoate (6.4 g, 98.3% yield) as a colorless oil.

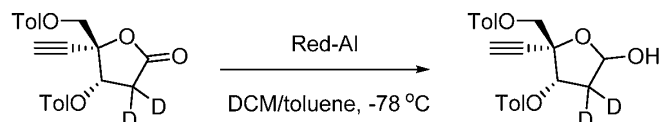
[000165] Preparation of [(2R,3S)-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyloxy)-5-oxo-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000166] To a mixture of [(2R,3S)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)-5-oxo-tetrahydrofuran-3-yl] 4-methylbenzoate (2 g, 7.24 mmol, 1 eq) in pyridine (15 mL) was added 4-methylbenzoyl chloride (1.68 g, 10.86 mmol, 1.5 eq). The resulting mixture was stirred at 0 °C for 16 h. Water (50 mL) was added at 0 °C, extracted with DCM (2 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, eluent with 0~15% ethyl

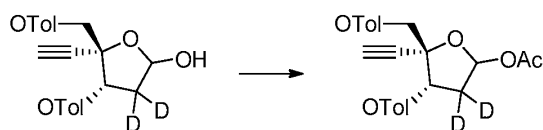
acetate/petroleum ether gradient @ 60 mL/min) to give [(2R,3S)-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-5-oxo-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (2.5 g, 87.6% yield) as a white solid.

[000167] Preparation of [(2R,3S)-4,4-dideuterio-2-ethynyl-5-hydroxy-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000168] To a solution of [(2R,3S)-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-5-oxo-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (2.5 g, 6.34 mmol, 1 eq) in DCM (16 mL) and toluene (36 mL) was added sodium bis(2-methoxyethoxy)aluminium hydride (2.75 g, 9.51 mmol, 2.64 mL, 70% purity, 1.5 eq) dropwise at -78 °C. The mixture was stirred at -78 °C for 2 h. The reaction was quenched by adding a solution of acetic acid (5 mL) in DCM (20 mL) over 10 min. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (50x3 mL), the combined organic layers were washed by brine (50 mL), dried over with Na₂SO₄, filtered and concentrated to give [(2R,3S)-4,4-dideuterio-2-ethynyl-5-hydroxy-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (2.5 g, 99.5% yield) as a light yellow liquid.

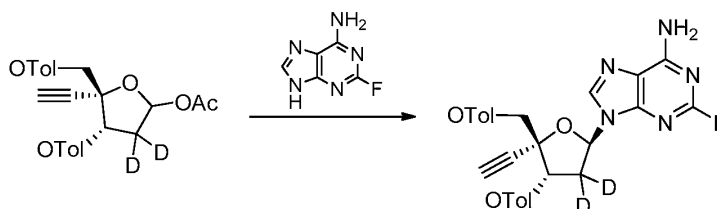
[000169] Preparation of [(2R,3S)-5-acetoxy-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000170] To a mixture of [(2R,3S)-4,4-dideuterio-2-ethynyl-5-hydroxy-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (2.5 g, 6.31 mmol, 1 eq) in toluene (25 mL) was added 4-(dimethylamino)pyridine (131 mg, 1.07 mmol, 0.17 eq) and TEA (747 mg, 7.38 mmol, 1.03 mL, 1.17 eq) at 0 °C, then acetic anhydride (644 mg, 6.31 mmol, 0.60 mL, 1 eq) was added. The resulting mixture was stirred at 0

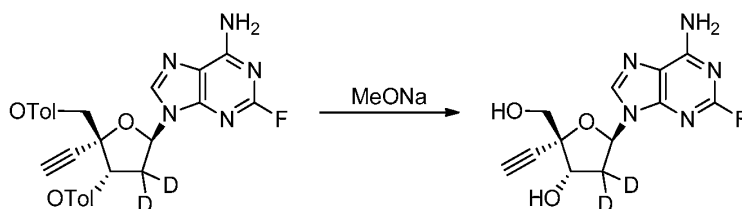
°C for 2 h. The reaction mixture was quenched with H₂O (10 mL). The resulting mixture was warmed to ambient temperature and washed sequentially with aqueous citric acid solution (10 wt%, 30 mL), aqueous sodium bicarbonate solution (5 wt%, 30 mL) and water (30 mL), the organic layer was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent with 0~20% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give [(2R,3S)-5-acetoxy-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (2.2 g, 79.6% yield) as a colorless oil.

[000171] Preparation of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



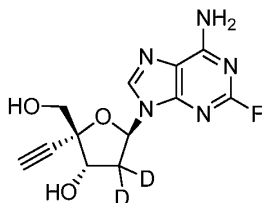
[000172] To a solution of 2-fluoro-9H-purin-6-amine (960 mg, 6.27 mmol, 1.25 eq) in MeCN (20 mL) was added Bis(trimethylsilyl)acetamide (3.06 g, 15.05 mmol, 3 eq). The mixture was stirred at 80 °C for 1 h. When the reaction mixture was cooled to 25 °C, TMSOTf (1.34 g, 6.02 mmol, 1.09 mL, 1.2 eq) was added and the reaction was stirred at 25 °C for 1 h, then [(2R,3S)-5-acetoxy-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (2.2 g, 5.02 mmol, 1 eq) in MeCN (15 mL) was added over 1 h at 80 °C and the mixture was stirred at 80 °C for 16 h. The DCM (50 mL) and H₂O (50 mL) was added, then the mixture was extracted with DCM (50x2 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent with 0~40% ethylacetate/DCM @ 30 mL/min) to give [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (1.43 g, 53.6% yield) as a light yellow solid.

[000173] Preparation of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol



[000174] To a mixture of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (1.4 g, 2.63 mmol, 1 *eq*) in THF (16 mL) was added NaOMe (1.42 g, 7.90 mmol, 30% purity, 3 *eq*) in MeOH (8 mL). The mixture was stirred at -25 °C for 3 h. The mixture was neutralized with AcOH (0.5 mL) and the mixture was concentrated under reduced pressure to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent with 0~10% methanol/dichloromethane gradient @ 30 mL/min) to give (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (710 mg, 91.3% yield) as a white solid.

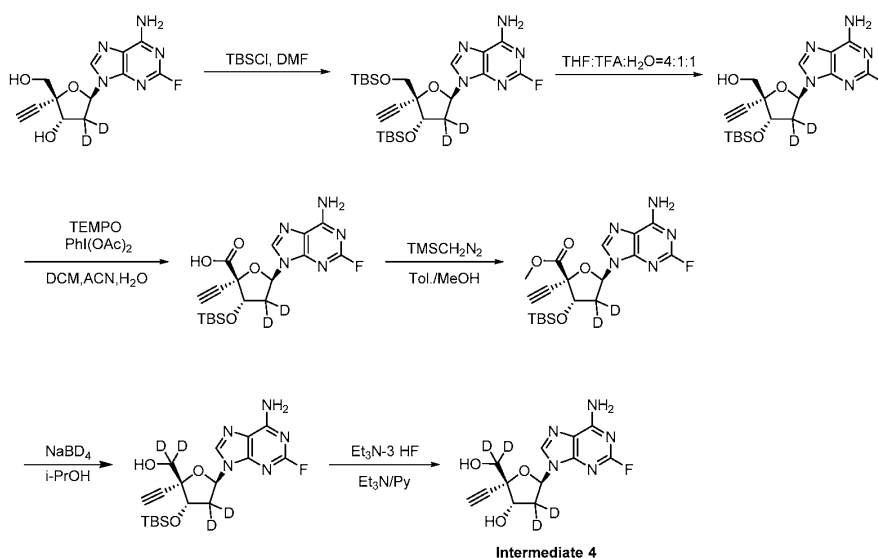
[000175] Purification of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol



[000176] (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (20 mg, 0.068 mmol, 1 *eq*) was purified by prep-TLC (SiO₂, DCM:MeOH = 10:1) to give (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (6.2 mg, 31.0% yield) as a white solid. LCMS (ESI) *m/z*, C₁₂H₁₀D₂FN₅O₃: calculated 295.10, found (M+H)⁺: 296.1. ¹H NMR (400MHz, CD₃CN) δ ppm 8.01 (s, 1H), 6.40-6.31 (m, 3H), 4.67 (d, *J* = 4.8Hz, 1H), 4.40-4.37 (m, 1H), 3.84-3.72 (m, 1H), 3.56 (d, *J* = 5.2Hz, 1H), 2.96 (s, 1H). ¹⁹F NMR (376MHz, CD₃CN) δ ppm -53.40 (s, 1F).

Intermediate 4:

(2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl-d2)tetrahydrofuran-4,4-d2-3-ol



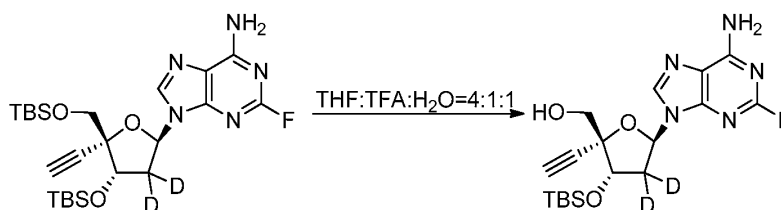
[000177] Preparation of 9-[(2R,4S,5R)-4-[tert-butyl(dimethyl)silyl]oxy-5-[[tert-butyl(dimethyl)silyl]oxymethyl]-3,3-dideuterio-5-ethynyl-tetrahydrofuran-2-yl]-2-fluoro-purin-6-amine



[000178] To a mixture of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (690 mg, 2.34 mmol, 1 *eq*) in DMF (3 mL) was added TBSCl (1.41 g, 9.36 mmol, 1.15 mL, 4 *eq*) and 1H-imidazole (956 mg, 14.04 mmol, 6 *eq*). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated and diluted with H₂O (30 mL) and extracted with EtOAc (30x3 mL). The combined organic layers were washed by brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash silica gel

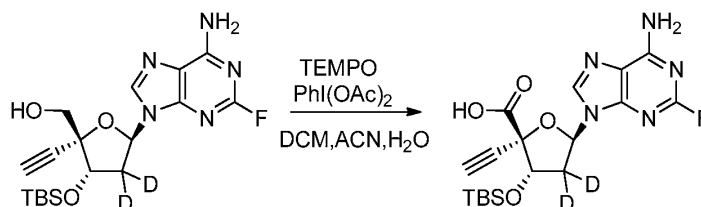
chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent with 0~10% methanol/dichloromethane gradient @ 20 mL/min) to give 9-[(2R,4S,5R)-4-[tert-butyl(dimethyl)silyl]oxy-5-[[tert-butyl(dimethyl)silyl]oxymethyl]-3,3-dideuterio-5-ethynyl-tetrahydrofuran-2-yl]-2-fluoro-purin-6-amine (1.1 g, 89.8% yield) as a white solid. LCMS (ESI) m/z for $C_{24}H_{38}D_2FN_5O_3Si_2$: calculated 523.3, found (M+H)⁺: 524.6.

[000179] Preparation of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-yl]methanol



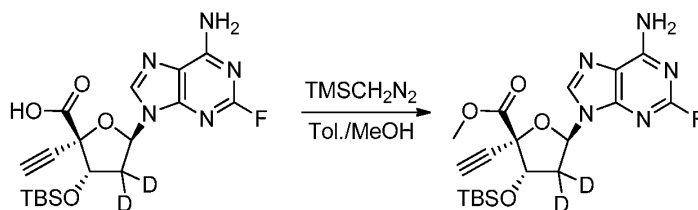
[000180] A mixture of 9-[(2R,4S,5R)-4-[tert-butyl(dimethyl)silyl]oxy-5-[[tert-butyl(dimethyl)silyl]oxymethyl]-3,3-dideuterio-5-ethynyl-tetrahydrofuran-2-yl]-2-fluoro-purin-6-amine (1.1 g, 2.10 mmol, 1 eq) in THF (12 mL), H₂O (3 mL), TFA (3 mL). The reaction mixture was stirred at 0 °C for 16 h. The resulting mixture was concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent with 0~10% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-yl]methanol (590 mg, 68.6% yield) as a white solid. LCMS (ESI) m/z for $C_{18}H_{24}D_2FN_5O_3Si$: calculated 409.19, found (M+H)⁺: 410.1.

[000181] Preparation of (2S,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-carboxylic acid



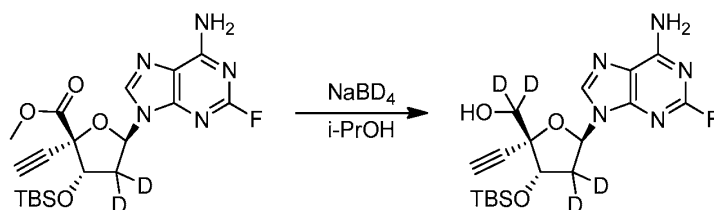
[000182] To a mixture of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-yl]methanol (590 mg, 1.44 mmol, 1 *eq*) in H₂O (0.05 mL) was added TEMPO (45 mg, 0.29 mmol, 0.2 *eq*) and PhI(OAc)₂ (557 mg, 1.73 mmol, 1.2 *eq*). The reaction mixture was stirred at 25 °C for 2 h, then DCM (10 mL) and CH₃CN (0.05 mL) was added. The resulting mixture was stirred at 25 °C for 14 h. The reaction mixture was filtered and the cake was washed by petroleum ether (5 mL), and then concentrated to give (2S,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-carboxylic acid (330 mg, 54.1% yield) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm) 8.30 (s, 1H), 7.87 (s, 2H), 6.34 (s, 1H), 4.94 (s, 1H), 3.66 (s, 1H), 0.92 (s, 9H), 0.13-0.12 (d, *J* = 4 Hz, 6H).

[000183] Preparation of methyl (2S,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-carboxylate



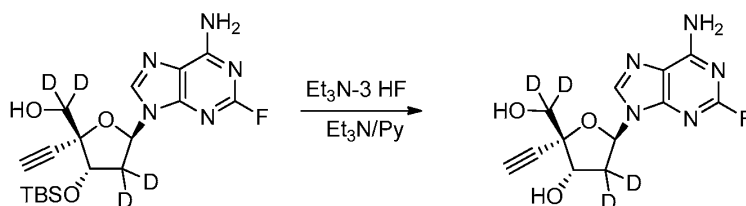
[000184] To a mixture of (2S,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-carboxylic acid (60 mg, 0.14 mmol, 1 *eq*) in toluene (4 mL) and MeOH (3.2 mL) was added TMSCHN₂ (2.0 M, 0.22 mL, 3 *eq*). The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent with 0~10% methanol/dichloromethane gradient @ 20 mL/min) to give methyl (2S,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-carboxylate (41 mg, 67% yield) as a white solid. LCMS (ESI) *m/z* for C₁₉H₂₄D₂FN₅O₄Si: calculated 437.54, found (M+H)⁺: 438.5. ¹H NMR (400MHz, CDCl₃) δ (ppm) 8.20 (s, 1H), 6.52 (s, 1H), 5.81 (s, 2H), 4.88 (s, 1H), 3.86 (s, 3H), 2.70 (s, 1H), 0.96 (s, 9H), 0.18-0.17 (d, *J* = 4 Hz, 6H). ¹⁹F NMR (376MHz, CDCl₃) δ (ppm) -50.588 (s, 1F).

[000185] Preparation of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-yl]-dideuterio-methanol



[000186] To a mixture of methyl (2S,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-carboxylate (150 mg, 0.34 mmol, 1 *eq*) in i-PrOH (8 mL) was added deuterated sodium borohydride (29 mg, 0.68 mmol, 2 *eq*) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent with 0~10% methanol/dichloromethane gradient @ 20 mL/min) to give [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-yl]-dideuterio-methanol (107 mg, 76.4% yield) as a white solid. ¹H NMR (400 MHz, CD₃CN) δ (ppm) 7.98 (s, 1H), 6.38 (s, 2H), 6.27 (s, 1H), 4.78 (s, 1H), 4.28 (s, 1H), 2.86 (s, 1H), 0.94 (s, 9H), 0.15-0.14 (d, *J* = 4 Hz, 6H). ¹⁹F NMR (376MHz, CD₃CN) δ (ppm) -53.40 (s, 1F).

[000187] Preparation of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-[dideuterio(hydroxy)methyl]-2-ethynyl-tetrahydrofuran-3-ol

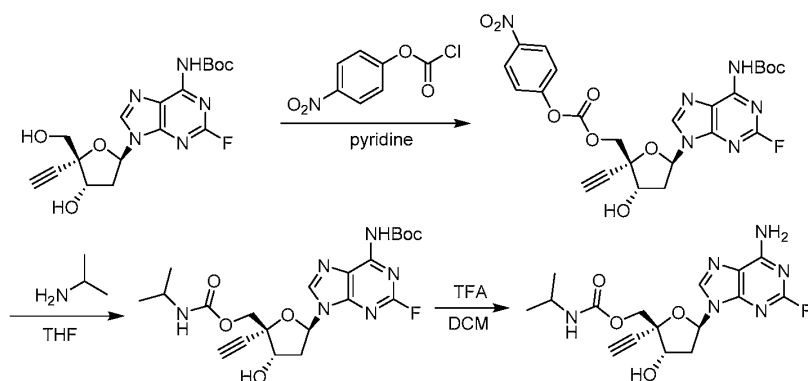


[000188] To a mixture of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-3-[tert-butyl(dimethyl)silyl]oxy-4,4-dideuterio-2-ethynyl-tetrahydrofuran-2-yl]-dideuterio-

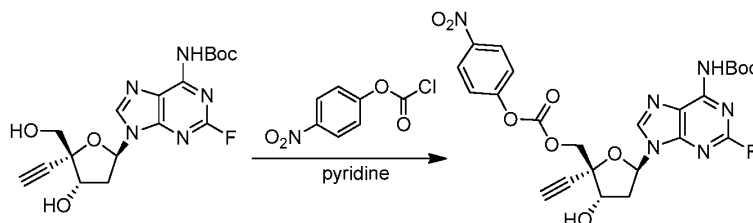
methanol (180 mg, 0.437 mmol, 1 *eq*) in pyridine (2.34 g, 29.28 mmol, 2.38 mL, 67 *eq*) and Et₃N (1.72 g, 17.04 mmol, 2.37 mL, 39 *eq*) was added N,N-diethylethanamine; trihydrofluoride (4.68 g, 29.06 mmol, 4.74 mL, 66.5 *eq*) at 0 °C. The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent with 0~10% methanol/dichloromethane gradient @20 mL/min) to give (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-[dideuterio(hydroxy)methyl]-2-ethynyl-tetrahydrofuran-3-ol (80 mg, 61.5% yield) as a white solid. LCMS (ESI) *m/z* for C₁₂H₈D₄FN₅O₃: calculated 297.12, found (M+H)⁺: 298.1. ¹H NMR (400MHz, DMSO-d₆) δ (ppm) 8.30 (s, 1H), 7.85 (s, 2H), 6.23 (s, 1H), 5.57-5.55 (d, *J* = 8 Hz, 1H), 5.25 (s, 1H), 4.56-4.55 (d, *J* = 4 Hz, 1H), 3.51 (s, 1H). ¹⁹F NMR (376MHz, DMSO-d₆) δ (ppm) -51.98 (s, 1F).

Example 1:

(2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate

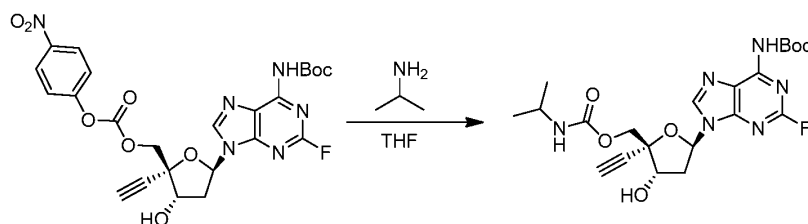


[000189] Preparation of [(2R,3S,5R)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl)methyl (4-nitrophenyl) carbonate



[000190] To a solution of tert-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate (80 mg, 0.203 mmol, 1 *eq*) in pyridine (0.8 mL) at 10 °C was added (4-nitrophenyl) carbonochloridate (41 mg, 0.203 mmol, 1 *eq*) at 10 °C. The mixture was stirred at 10 °C for 16 hr, added water (10 mL) and extracted with EtOAc (10 mL). The organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the crude product [(2*R*,3*S*,5*R*)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (4-nitrophenyl) carbonate (114 mg, crude) as a yellow oil, which was used for next reaction without further purification. LCMS (ESI) *m/z*, C₂₄H₂₃FN₆O₉: calculated 558.2, measured (M+H)⁺: 559.1.

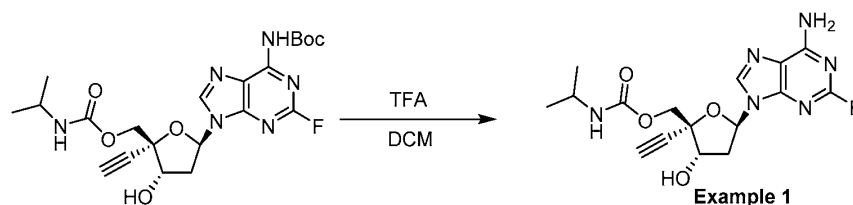
[000191] Preparation of tert-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(isopropylcarbamoyloxymethyl)tetrahydrofuran-2-yl]-2-fluoropurin-6-yl]carbamate



[000192] To a mixture of [(2*R*,3*S*,5*R*)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (4-nitrophenyl) carbonate (10 mg, 0.018 mmol, 1 *eq*) and triethylamine (3.6 mg, 0.035 mmol, 2 *eq*) in THF (0.5 mL) was added propan-2-amine (1.3 mg, 0.021 mmol, 1.2 *eq*). The mixture was stirred at 15 °C for 2.5 hr, added water (5 mL) and extracted with EtOAc (2 x 10 mL). The organic layers were concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*30 10u; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 15%-45%, 11min) to give tert-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(isopropylcarbamoyloxymethyl)tetrahydrofuran-2-yl]-2-fluoropurin-6-yl]carbamate

(3.6 mg, 45.0% yield) as a white solid. LCMS (ESI) m/z , $C_{21}H_{27}FN_6O_6$: calculated 478.2, measured $(M+H)^+$: 479.3; $(M+Na)^+$: 501.2.

[000193] Preparation of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate

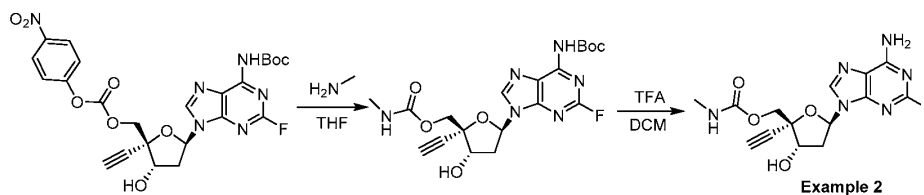


[000194] To a solution of tert-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(isopropylcarbamoyloxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate (3.6 mg, 0.0075 mmol, 1 *eq*) in DCM (0.5 mL) was added TFA (77 mg, 0.68 mmol, 0.05 mL, 89.8 *eq*) at 10 °C. The mixture was stirred at 10 °C for 40 hr. The mixture was concentrated under reduced pressure and purified by prep-HPLC (column: Agela DuraShell 150mmx25mmx5um; mobile phase: [water (0.05% HCl)-ACN]; B%: 10%-40%, 8min) to give ((2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate (1.2 mg, 40.0% yield) as a white solid. LCMS (ESI) m/z , $C_{16}H_{19}FN_6O_4$: calculated 378.2, measured $(M+H)^+$: 379.3; $(M+Na)^+$: 401.2. 1H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.27 (s, 1H), 7.85 (br s, 2H), 7.13 (br d, J = 4.8 Hz, 1H), 6.24 (dd, J = 7.6, 5.2 Hz, 1H), 4.55 (br t, J = 6.8 Hz, 1H), 4.35 (br d, J = 11.6 Hz, 1H), 4.00 (br d, J = 11.6 Hz, 1H), 3.61 (s, 1H), 2.70-2.79 (m, 1H), 2.40-2.43 (m, 1H), 0.98-1.07 (m, 7H). ^{19}F NMR (376 MHz, DMSO-*d*₆) δ (ppm) -51.79 (s).

Example 2:

((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate

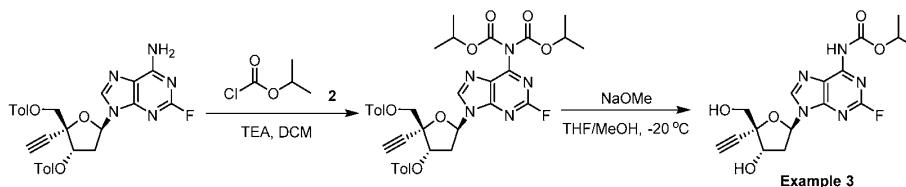
Preparation of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate



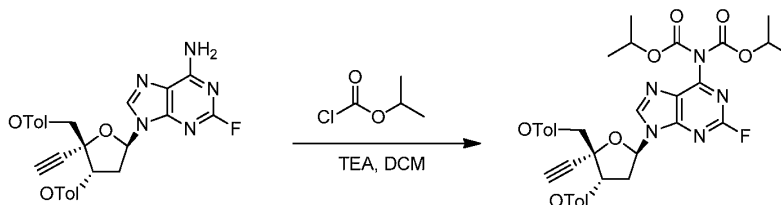
[000195] ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methyl carbamate was prepared using the same procedure as ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropyl carbamate except replacing propan-2-amine with methylamine. LCMS (ESI) m/z , $C_{14}H_{15}FN_6O_4$: calculated 350.1, measured $(M+H)^+$: 351.2. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.26 (s, 1H), 7.87 (br s, 2H), 7.13 (br d, $J=4.4$ Hz, 1H), 6.24 (dd, $J=7.6, 5.0$ Hz, 1H), 5.76 (br d, $J=4.4$ Hz, 1H), 4.55 (br d, $J=5.2$ Hz, 1H), 4.35 (d, $J=11.6$ Hz, 1H), 4.03 (d, $J=11.6$ Hz, 1H), 3.60 (s, 1H), 2.70-2.79 (m, 1H), 2.54 (s, 3H), 2.40-2.45 (m, 1H). ^{19}F NMR (376 MHz, $DMSO-d_6$) δ (ppm) -51.75 (s).

Example 3:

isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate

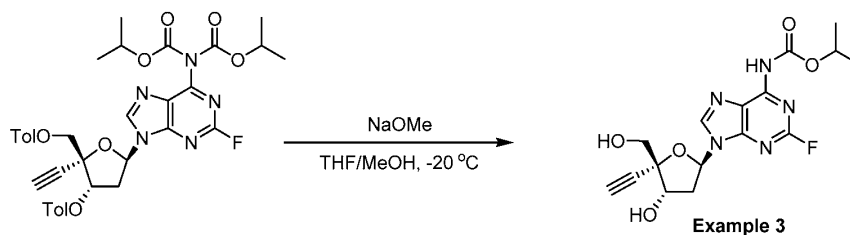


Preparation of (2R, 3S, 5R)-5-[6-[bis(isopropoxycarbonyl)amino]-2-fluoro-9H-purin-9-yl]-2-ethynyl-2-(((4-methylbenzoyl)oxy)methyl)-tetrahydrofuran-3-yl 4-methylbenzoate



[000196] To a mixture of [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-(4-methylbenzoyloxy)-tetrahydrofuran-2-yl)methyl 4-methylbenzoate (50 mg, 0.094 mmol, 1 *eq*) and Et₃N (10 mg, 0.094 mmol, 1 *eq*) in DCM (1 mL) was added isopropyl carbonochloridate (23 mg, 0.19 mmol, 2 *eq*) at 0 °C, the mixture was stirred at 15 °C for 16 hr. The mixture was concentrated under reduced pressure and 2 mL of water was added, extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (20 mL) and concentrated under reduced pressure to give (2*R*,3*S*,5*R*)-5-(6-(bis(isopropoxycarbonyl)amino)-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(((4-methylbenzoyloxy)methyl)tetrahydrofuran-3-yl) 4-methylbenzoate as a crude product, which was used into the next reaction without further purification. LCMS (ESI) *m/z*, C₃₆H₃₆FN₅O₉: calculated 701.3, measured (M+H)⁺: 702.1.

Preparation of isopropyl (9-((2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate

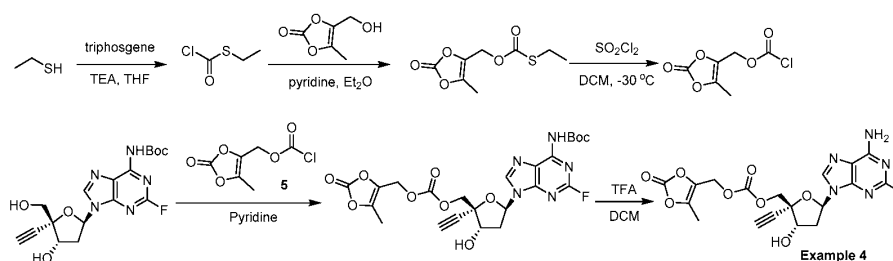


[000197] To a solution of (2*R*, 3*S*, 5*R*)-5-[6-[bis(isopropoxycarbonyl)amino]-2-fluoro-9H-purin-9-yl]-2-ethynyl-2-(((4-methylbenzoyloxy)methyl)tetrahydrofuran-3-yl) 4-methylbenzoate (66 mg, 0.094 mmol) in THF (1 mL) was at -20 °C added NaOMe (34 mg, 0.19 mmol, 30%, 2 *eq*) and the resulting mixture was stirred for 16 hr at -20 °C. Additional NaOMe (17 mg, 0.095 mmol, 30%, 1 *eq*) was added and the mixture was stirred at -20 °C for another 40 hr. The mixture was neutralized with AcOH (0.1 mL), concentrated under reduced pressure, and purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0–8% MeOH/DCM gradient @ 20 mL/min) and again by prep-HPLC (column: Waters Xbridge Prep OBD C18 150x30 5u; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 5%-30%, 7min) to give isopropyl (9-((2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-

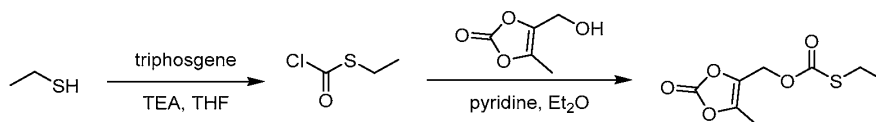
(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate (3.5 mg, 11% yield) as a white solid. LCMS (ESI) m/z , $C_{16}H_{18}FN_5O_9$: calculated 379.1 (measured $(M+Na)^+$: 402.1). 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 (s, 1H), 7.98 (s, 2H), 6.41 (dd, $J=8.8, 5.6$ Hz, 1H), 5.13 (dt, $J=12.4, 6.4$ Hz, 1H), 5.04 (dd, $J=11.0, 3.0$ Hz, 1H), 4.70-4.75 (m, 1H), 4.09 (dd, $J=12.4, 2.4$ Hz, 1H), 3.84-3.93 (m, 1H), 3.06-3.15 (m, 1H), 2.83 (s, 1H), 2.48-2.56 (m, 2H), 1.36 (d, $J=6.0$ Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -46.89 (s).

Example 4 (Method 1):

((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate



Preparation of S-ethyl O-((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonothioate

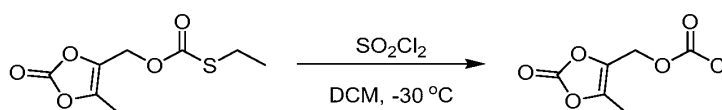


[000198] To a mixture of ethanethiol (16 g, 257.5 mmol, 19.1 mL, 1 *eq*), triethyl amine (26.1 g, 257.5 mmol, 35.8 mL, 1 *eq*) in THF (1 L) at -15 °C was added bis(trichloromethyl) carbonate (76.4 g, 257.5 mmol, 1 *eq*) in THF (50 mL). The mixture was warm up to 18 °C and stirred at 18 °C for 2 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give S-ethyl chloromethanethioate (13 g,

crude) as a yellow oil which was used for the next reaction directly without further purification.

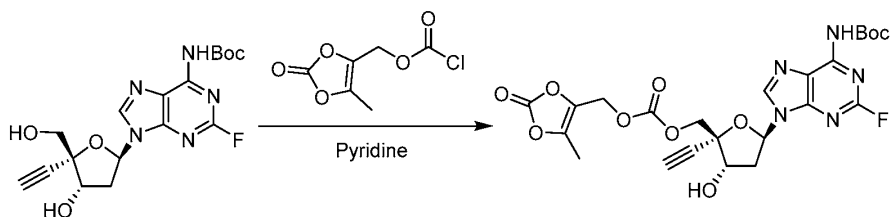
[000199] To a mixture of 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (13 g, 99.9 mmol, 1 *eq*) in Et₂O (800 mL) at 0 °C was added pyridine (7.90 g, 99.9 mmol, 8.1 mL, 1 *eq*) and S-ethyl chloromethanethioate (12.45 g, 99.9 mmol, 1.0 *eq*) in Et₂O (200 mL), the mixture was stirred at 0 °C for 1 h and warm up to 18 °C and stirred at 18 °C for 16 h. The mixture was filtered and concentrated in vacuo, and then taken up in DCM (150 mL) and washed with sat aq. NaHCO₃ (150 mLx2), water (150 mLx2). The mixture was concentrated under reduced pressure and purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~15% ethyl acetate/petroleum ether gradient @ 70 mL/min) to give (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ethylsulfanylformate (9.2 g, 42.2% yield) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.95 (s, 2H), 2.89 (q, *J*=7.2 Hz, 2H), 2.19 (s, 3H), 1.32 (t, *J*=7.2 Hz, 3H).

Preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonochloridate



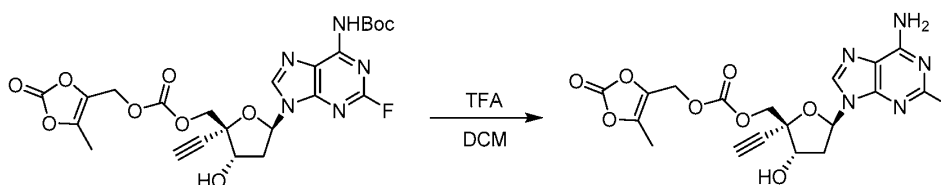
[000200] To a mixture of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ethylsulfanylformate (500 mg, 2.29 mmol, 1 *eq*) in DCM (50 mL) was added sulfuryl chloride (618.5 mg, 4.58 mmol, 0.46 mL, 2 *eq*). The resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was washed with water (50 mL x 2), 5% aq Na₂CO₃ (50 mL x2), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonochloridate (350 mg, crude) as a yellow oil. The product was dissolved in 10 mL DCM and stored in refrigerator.

Preparation of tert-butyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-((((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)oxy)methyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate



[000201] To a mixture of tert-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate (100 mg, 0.25 mmol, 1 *eq*) in pyridine (2 mL) at 20 °C was added (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonochloridate (140 mg, 0.73 mmol, 4 mL, 2.86 *eq*, 35 mg/mL in DCM), the mixture was stirred at 20 °C for 16 hr. The mixture was concentrated under reduced pressure, and purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~5% MeOH/DCM gradient @25 mL/min) to give [(2*R*,3*S*,5*R*)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (45 mg, 32.2% yield) as a yellow solid. LCMS (ESI) *m/z*, C₂₃H₂₄FN₅O₁₀: calculated 549.2, measured (M+H)⁺: 550.1.

Preparation of ((2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-9*H*-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate



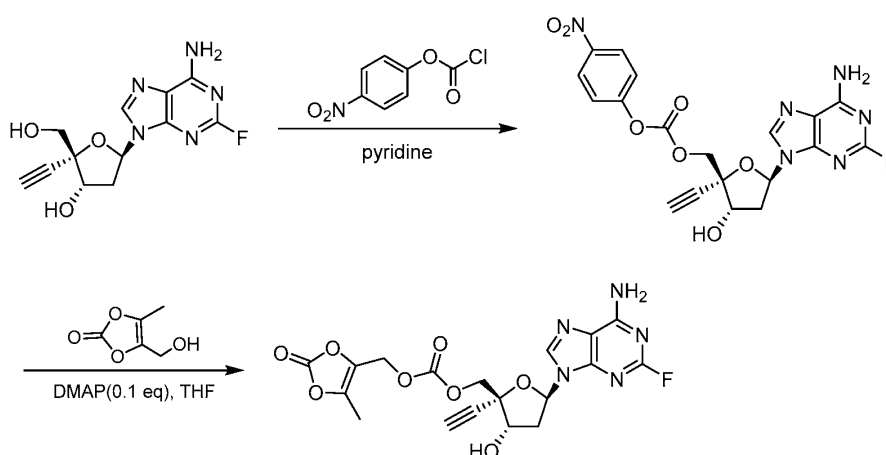
**Example 4
Method 1**

[000202] To a mixture of [(2*R*,3*S*,5*R*)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (45 mg, 0.082 mmol, 1 *eq*) in toluene (1 mL) at 20 °C was added TFA (154 mg, 1.35 mmol, 0.1 mL, 16.5 *eq*). The mixture was stirred at 20 °C for 16 hr and then was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Boston Green ODS 150x30mmx5μm; mobile phase:

[water (0.2%FA)-ACN]; B%: 13%-43%, 8min) to give ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate (11 mg, 25.4% yield) as a white solid. LCMS (ESI) m/z , $C_{18}H_{16}FN_5O_6$: calculated 449.1, measured $(M+H)^+$: 450.1. ^{19}F NMR (376 MHz, CD_3OD) δ (ppm) -53.00 (s). 1H NMR (400MHz, CD_3CN) 7.92 (s, 1H), 6.41 - 6.21 (m, 3H), 4.87 (d, $J= 5.2$ Hz, 2H), 4.77 - 4.67 (m, 1H), 4.51 (d, $J= 11.6$ Hz, 1H), 4.30 (d, $J= 11.6$ Hz, 1H), 3.75 (d, $J= 6.4$ Hz, 1H), 3.00 (s, 1H), 2.89 - 2.81 (m, 1H), 2.61 - 2.52 (m, 1H), 2.10 (s, 3H).

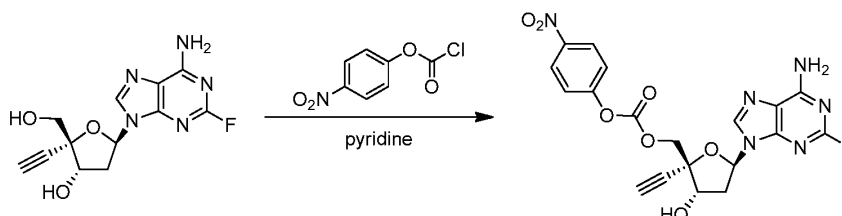
Example 4 (Method 2):

((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate



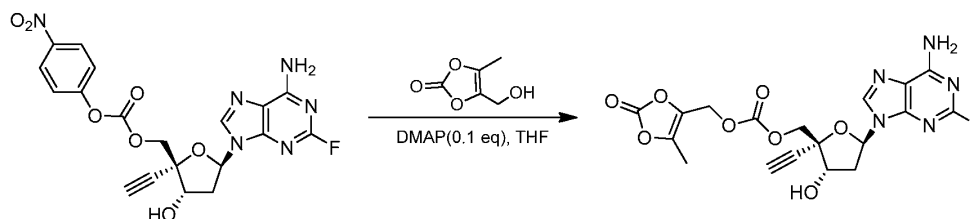
Example 4 Method 2

[000203] Preparation of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (4-nitrophenyl) carbonate



[000204] To a mixture of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (100 mg, 0.34 mmol, 1 *eq*) in pyridine (5 mL) was added (4-nitrophenyl) carbonochloridate (82 mg, 0.41 mmol, 1.2 *eq*), the mixture was stirred at 26 °C for 16 h. (4-nitrophenyl) carbonochloridate (82 mg, 0.41 mmol, 1.2 *eq*) was added and the mixture was stirred at 26 °C for 24 h. The reaction solution was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~5% DCM/MeOH gradient @ 25 mL/min) to give [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (4-nitrophenyl) carbonate (80 mg, 51.2% yield) as a white solid. LCMS (ESI) *m/z*, C₁₉H₁₅FN₆O₇: calculated 458.4, found (M+H)⁺: 459.1.

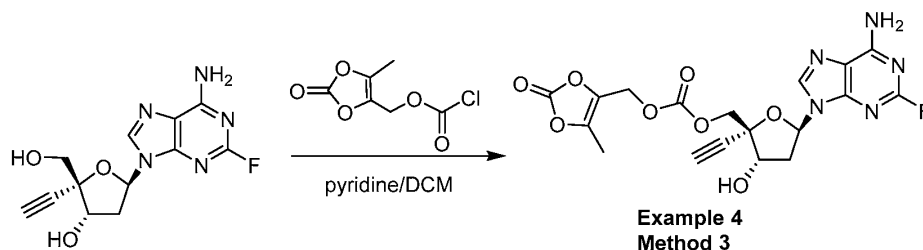
[000205] Preparation of((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate



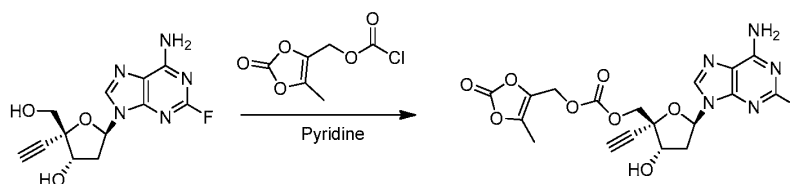
[000206] To a mixture of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (4-nitrophenyl) carbonate (150 mg, 0.298 mmol, 1 *eq*) and 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (96 mg, 0.745 mmol, 2.5 *eq*) in THF (3 mL) was added DMAP (3.6 mg, 0.023 mmol, 0.1 *eq*), the mixture was stirred at 25 °C for 2 h. The reaction solution was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~2.5% DCM/MeOH gradient @ 25 mL/min) to give [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (85 mg, 63.5% yield) as a white solid. LCMS (ESI) *m/z*, C₁₈H₁₆FN₅O₈ calculated 449.4, found 450.1 (M+H)⁺. ¹H NMR (400MHz, CD₃CN) δ (ppm) 7.91 (s, 1H), 6.42 - 6.16 (m, 3H), 4.93 - 4.79 (m, 2H), 4.76 - 4.67 (m, 1H), 4.53 - 4.46 (m, 1H), 4.34 - 4.25 (m, 1H), 3.77 - 3.69 (m, 1H), 3.00 (s, 1H), 2.90 - 2.78 (m,

1H), 2.62 - 2.50 (m, 1H), 2.10 (s, 3H). ^{19}F NMR (376MHz, CD_3CN) δ (ppm) -52.87 (s, 1F).

Example 4 (Method 3):
((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate



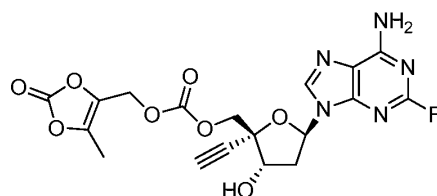
[000207] Preparation of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (4-nitrophenyl) carbonate



[000208] To a mixture of ((2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (5 g, 17.05 mmol, 1 eq) in pyridine (50 mL) was dropwise added (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonochloridate (16.42 g, 85.25 mmol, 5 eq) in DCM (16 mL) at 0 °C over a period of 2 h, after that the mixture was stirred at 16 °C for 10 min. The mixture was diluted with DCM (200 mL) and washed with water (150 mL), brine (150 mL x 2), dried over Na_2SO_4 , filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~5% MeOH/DCM gradient @ 65 mL/min) to give ((2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl)methyl (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (5.10 g, 11.35 mmol, 66.6% yield) as a light yellow solid. LCMS (ESI) m/z , $\text{C}_{18}\text{H}_{16}\text{FN}_5\text{O}_8$: calculated 449.4, found $(\text{M}+\text{H})^+$: 450.1. ^1H NMR (400MHz, CD_3CN) δ

(ppm) 7.92 (s, 1H), 6.34 (br s, 2H), 6.29-6.23 (m, 1H), 4.93-4.81 (m, 2H), 4.77-4.69 (m, 1H), 4.51 (d, $J = 11.6$ Hz, 1H), 4.30 (d, $J = 11.6$ Hz, 1H), 3.74 (d, $J = 6.4$ Hz, 1H), 3.00 (s, 1H), 2.91-2.79 (m, 1H), 2.62-2.51 (m, 1H), 2.10 (s, 3H). ^{19}F NMR (376MHz, CD_3CN) δ (ppm) -52.84 (s, 1F).

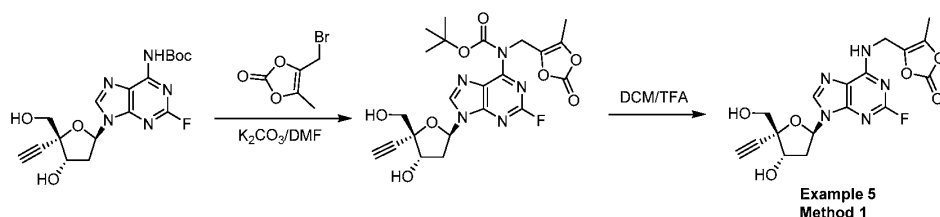
[000209] Recrystallization of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (4-nitrophenyl) carbonate



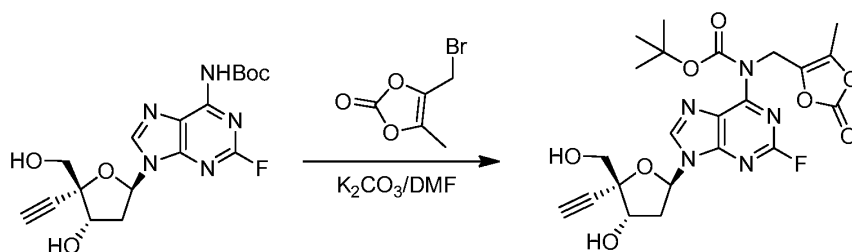
[000210] A mixture of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (9.5 g, 21.14 mmol, 1 eq) in MeCN (50 mL) and EtOAc (50 mL) was heated at 80 °C for 30 min and dissolution of the solids was observed. After cooling to room temperature (20 °C), the mixture was stirred at 20 °C for 16 h. The mixture was filtered and the filter cake was dried in vacuum to give [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (8.0 g, 17.80 mmol, 84.2% yield) as a white solid. LCMS (ESI) m/z , $\text{C}_{18}\text{H}_{16}\text{FN}_5\text{O}_8$: calculated 449.4, found $(\text{M}+\text{H})^+$: 450.1. ^1H NMR (400MHz, CD_3CN) δ (ppm) 7.92 (s, 1H), 6.31 (br s, 2H), 6.27-6.24 (m, 1H), 4.92-4.81 (m, 2H), 4.77-4.69 (m, 1H), 4.51 (d, $J = 11.6$ Hz, 1H), 4.30 (d, $J = 11.6$ Hz, 1H), 3.73 (d, $J = 6.4$ Hz, 1H), 3.00 (s, 1H), 2.89-2.81 (m, 1H), 2.62-2.51 (m, 1H), 2.10 (s, 3H). ^{19}F NMR (376MHz, CD_3CN) δ (ppm) -52.84 (s, 1F).

Example 5 (Method 1):

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



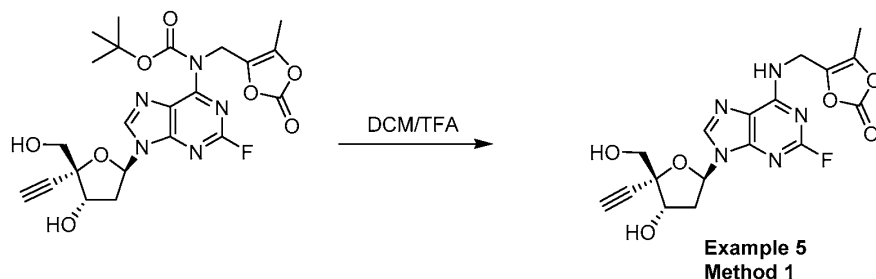
Preparation of tert-butyl(9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)carbamate



[000211] To a mixture of tert-butyl N-[9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-purin-6-yl]carbamate (100 mg, 0.25 mmol, 1 *eq*) in DMF (5 mL) was added K₂CO₃ (70 mg, 0.51 mmol, 2 *eq*) and 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one (147 mg, 0.76 mmol, 3 *eq*). The reaction mixture was then heated at 60°C for 12 hr, concentrated and then diluted with H₂O (30 mL). The resulting mixture was extracted with EtOAc (30 x3 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% methanol/dichloromethane gradient @30 mL/min) to give tert-butyl N-[9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-purin-6-yl]-N-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]carbamate (45 mg, 35.0% yield) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.02 (s, 1H), 6.40-6.43 (m, 1H), 5.02 (s, 2H), 4.70-4.73 (m, 2H), 4.09 (d, J = 12 Hz, 1H), 3.90-3.92 (m, 1H), 3.11-3.14 (m, 1H), 2.85 (s, 1H), 2.50-2.55 (m, 1H), 2.45 (bs, 1H), 2.22 (s, 3H), 1.53 (s, 9H).

Preparation of 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-

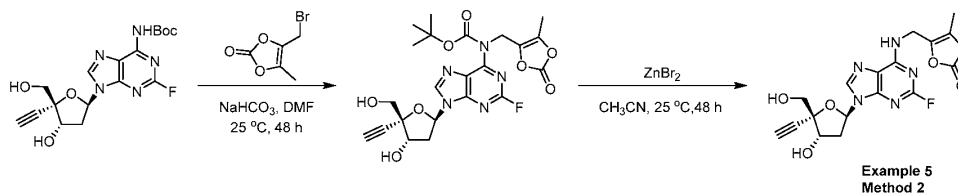
(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one



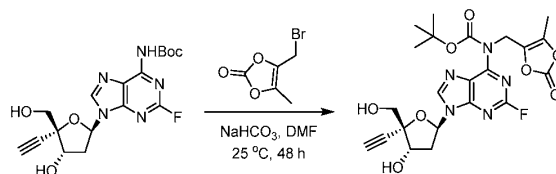
[000212] To a solution of tert-butyl N-[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]-N-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]carbamate (40 mg, 0.079 mmol, 1 *eq*) in dichloromethane (DCM) (3 mL) at 25 °C was added TFA (0.5 mL). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was concentrated and purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(0.2%FA)-ACN]:B%: 15%-45%,8min) to give 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one (1.7 mg, 5% yield) as a white solid. LCMS (ESI) *m/z*, C₁₇H₁₆FN₅O₆: calculated 405.1, measured (M+H)⁺: 406.1. (M+Na)⁺: 428.1. ¹H NMR (400 MHz, CD₃OD) δ (ppm) 8.26 (s, 1H), 6.38-6.35 (m, 1H), 4.76-4.72 (m, 1H), 4.51 (s, 1H), 3.87-3.84 (d, *J* = 12 Hz, 1H), 3.78-3.75 (d, *J* = 12 Hz, 1H), 3.09 (s, 2H), 2.80-2.75 (m, 1H), 2.64-2.57 (m, 1H), 2.24 (s, 3H). ¹⁹F NMR (376 MHz, CD₃OD) δ (ppm) -53.00.

Example 5 (Method 2):

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

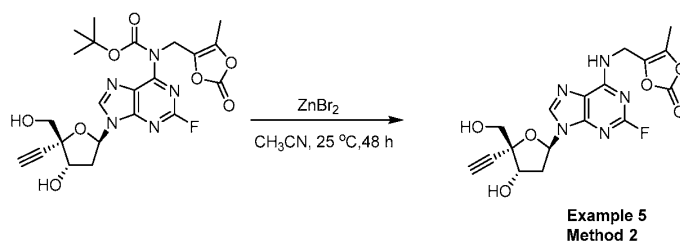


[000213] Preparation of *tert*-butyl-*N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]-*N*-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]carbamate



[000214] To a solution of *tert*-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate (300 mg, 0.76 mmol, 1 *eq*) in DMF (5 mL) was added NaHCO₃ (128 mg, 1.52 mmol, 2 *eq*), then 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one (294 mg, 1.52 mmol, 2 *eq*) was added. The mixture was stirred at 25 °C for 48 h. The mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent with 0~100% ethyl acetate/petroleum ether gradient @ 20 mL/min) to give *tert*-butyl *N*-[9-[(2*R*,4*S*, 5*R*)-5ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]-*N*-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]carbamate (200 mg, 52% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.98 (s, 1H), 6.45-6.33 (m, 1H), 4.99 (s, 1H), 5.03-4.94 (m, 1H), 4.78 (br d, *J* = 11.2 Hz, 1H), 4.71 (br s, 1H), 4.16-4.02 (m, 2H), 3.11 (br s, 1H), 2.80 (s, 1H), 2.49 (br d, *J* = 7.2 Hz, 1H), 2.42 (br s, 1H), 2.19 (s, 3H), 1.55 (s, 9H).

[000215] Preparation of 4-[[[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]amino]methyl]-5-methyl-1,3-dioxol-2-one

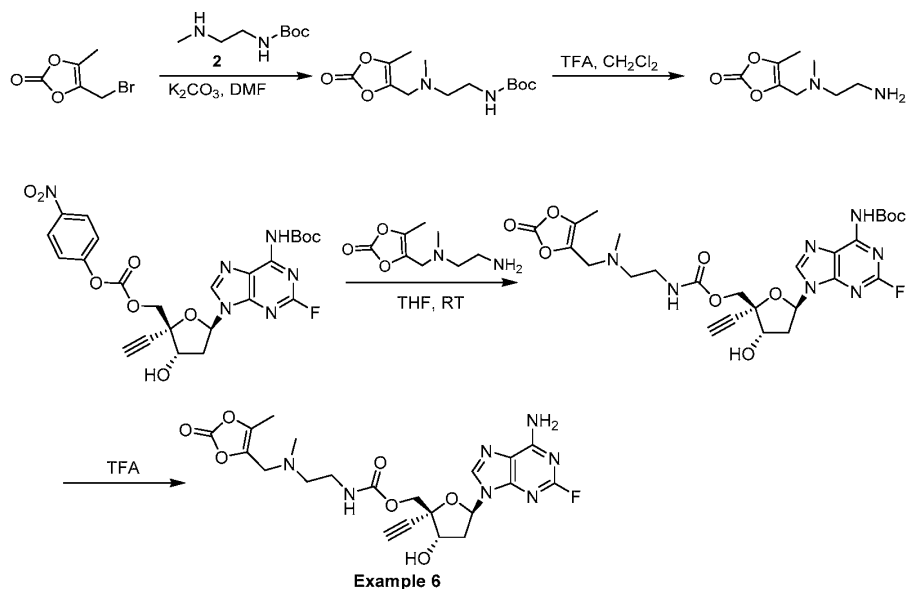


[000216] To a solution of *tert*-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]-*N*-[(5-methyl-2-oxo-1,3-

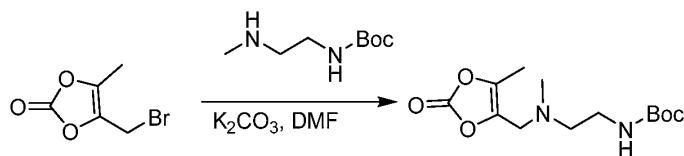
dioxol-4-yl)methyl]carbamate (50 mg, 0.10 mmol, 1 *eq*) in CH₃CN (5 mL) was added ZnBr₂ (45 mg, 0.20 mmol, 2 *eq*). The mixture was stirred at 25 °C for 48 h. The reaction was filtered, and the filtrate was concentrated. The resulting residue was purified by prep-HPLC (FA condition; column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.2%FA)-ACN]; B%: 22%-52%, 6 min) to give 4-[[[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]amino]methyl]-5-methyl-1,3-dioxol-2-one (19.8 mg, 48.8% yield) as a white solid. LCMS (ESI) *m/z*, C₁₇H₁₆FN₅O₆: calculated 405.34, found (M+H)⁺: 406.1. ¹H NMR (400 MHz, CD₃OD) δ (ppm) 8.26 (s, 1H), 6.38-6.35 (m, 1H), 4.76-4.72 (m, 1H), 4.51 (br s, 2H), 3.87-3.84 (d, *J* = 12 Hz, 1H), 3.78-3.75 (d, *J* = 12 Hz, 1H), 3.09 (s, 1H), 2.80-2.75 (m, 1H), 2.64-2.57 (m, 1H), 2.24 (s, 3H). ¹⁹F NMR (376 MHz, CD₃OD) δ (ppm) -52.33.

Example 6:

((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate

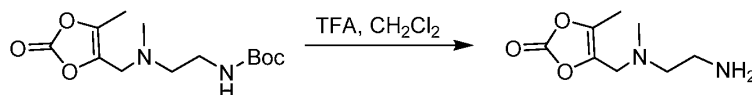


Preparation of tert-butyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate



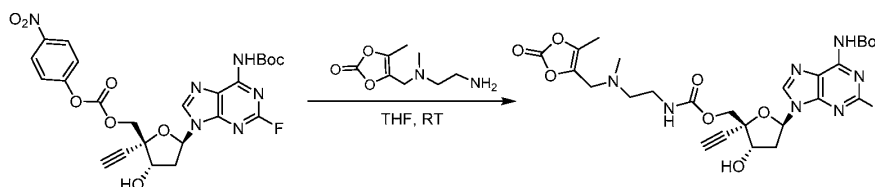
[000217] To a mixture of tert-butyl N-[2-(methylamino)ethyl]carbamate (451 mg, 2.59 mmol, 1 *eq*) and K₂CO₃ (393.9 mg, 2.85 mmol, 1.1 *eq*) in DMF (15 mL) was added 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one (500 mg, 2.59 mmol, 1 *eq*), the mixture was stirred at 20 °C for 16 hr. The mixture was concentrated under reduced pressure, purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0-20% ethyl acetate/petroleum ether gradient @30 mL/min) to give tert-butyl N-[2-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]amino]ethyl]carbamate (500 mg, 1.75 mmol, 67.4% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 6.65 (m, 1H), 3.37 (s, 2H), 2.99 (m, 2H), 2.39 (m, 2H), 2.18 (s, 3H), 2.09 (s, 3H), 1.37 (s, 9H).

Preparation of 4-(((2-aminoethyl)(methyl)amino)methyl)-5-methyl-1,3-dioxol-2-one



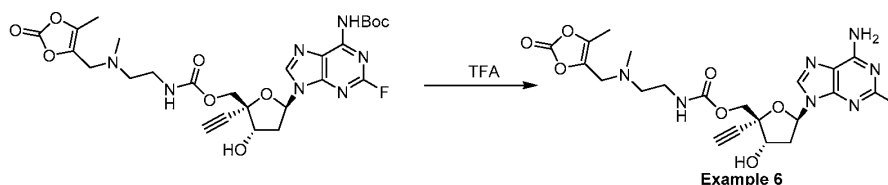
[000218] To a mixture of tert-butyl N-[2-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]amino]ethyl]carbamate (200 mg, 0.699 mmol, 1 *eq*) in dichloromethane (2 mL) at 20 °C was added TFA (1.54 g, 13.51 mmol, 1 mL, 19.34 *eq*), the mixture was stirred at 20 °C for 16 hr. The mixture was concentrated under reduced pressure to give 4-[[2-aminoethyl(methyl)amino]methyl]-5-methyl-1,3-dioxol-2-one (120 mg, crude, 3TFA) as a yellow oil. LCMS (ESI) *m/z*, C₈H₁₄N₂O₃: calculated 186.1, measured (M+H)⁺: 187.2.

Preparation tert-butyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(((2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamoyl)oxy)methyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate



[000219] To a mixture of [(2R,3S,5R)-5-[6-(tert-butoxycarbonylamino)-2-fluoropurin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (4-nitrophenyl) carbonate (34 mg, 0.060 mmol, 1 *eq*) and triethyl amine (30 mg, 0.30 mmol, 5 *eq*) in dichloromethane (2 mL) at 20 °C was added 4-[[2-aminoethyl(methyl)amino]methyl]-5-methyl-1,3-dioxol-2-one (38 mg, 0.072 mmol, 1.2 *eq*, 3TFA), the mixture was stirred at 20 °C for 16 hr. The mixture was then concentrated under reduced pressure and purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~5% dichloromethane /MeOH gradient @25 mL/min) to give tert-butyl N-[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-[2-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]amino]ethyl]carbamoyloxy]methyl]tetrahydrofuran-2-yl]-2-fluoropurin-6-yl]carbamate (34 mg, 92.1% yield) as a yellow solid. LCMS (ESI) *m/z*, C₂₆H₃₂FN₇O₉: calculated 605.2, measured (M+Na)⁺: 628.2.

Preparation of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl(2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate

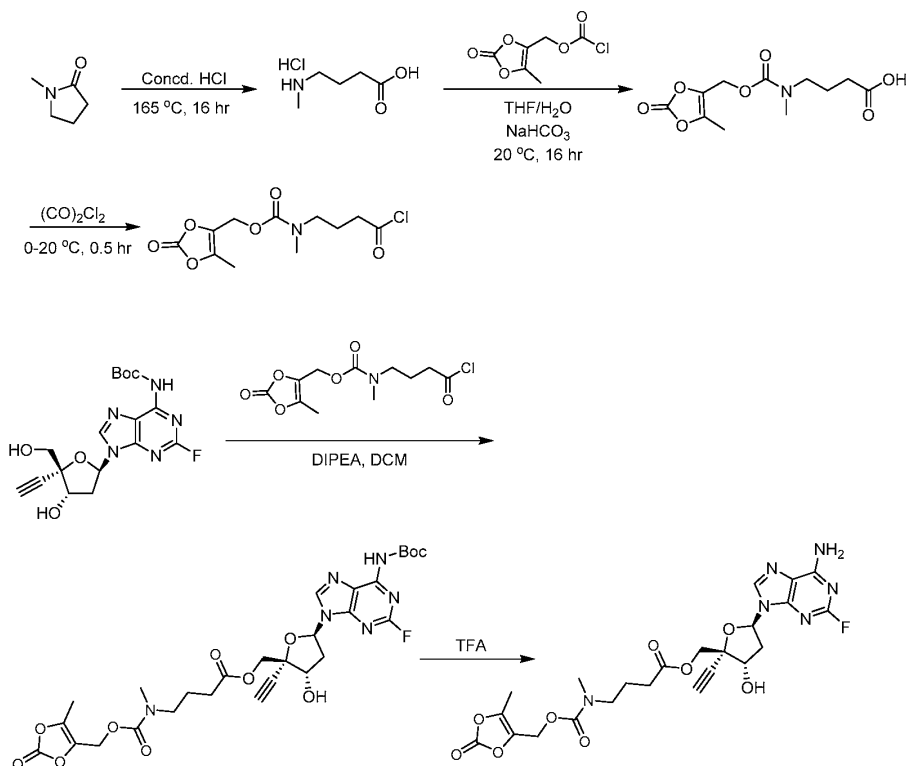


[000220] To a mixture of tert-butyl N-[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-[2-

[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]amino]ethylcarbamoyloxymethyl]tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate (34 mg, 0.055 mmol, 1 eq) in toluene (1 mL) was added TFA (129 mg, 1.13 mmol, 0.084 mL, 20.45 eq), the mixture was stirred at 20 °C for 16 hr. The mixture was concentrated under reduced pressure and purified by prep-HPLC (column: Phenomenex Gemini-NX 150x30mmx5um; mobile phase: [water (0.05% HCl)-ACN]; B%: 0%-30%, 7min), and then re-purified by prep-HPLC (column: Welch Xtimate C18 150x25mmx5um; mobile phase: [water (0.2% FA)-ACN]; B%: 1%-20%, 8min) to give 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one (2.0 mg, 20.0% yield) as a white solid. LCMS (ESI) m/z, C₂₁H₂₄FN₇O₇: calculated 505.2, measured (M+H)⁺: 506.3, (M+Na)⁺: 528.2. ¹H NMR (400 MHz, CD₃OD) δ (ppm) 8.15 (s, 1H), 6.32 (dd, J=8.0, 4.0 Hz, 1H), 4.80 (m, 1H), 4.47 (d, J=11.6 Hz, 1H), 4.24 (d, J=11.6 Hz, 1H), 3.45 (s, 2H), 3.19 (t, J=6.8, 2H), 3.17 (s, 1H), 2.84 (m, 1H), 2.66 (m, 1H), 2.51 (t, J=6.8, 2H), 2.30 (s, 3H), 2.14 (s, 3H). ¹⁹F NMR (376 MHz, CD₃OD) δ (ppm) -52.93 (s).

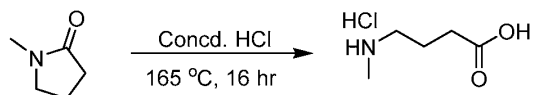
Example 7:

((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl 4-(methyl(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)butanoate



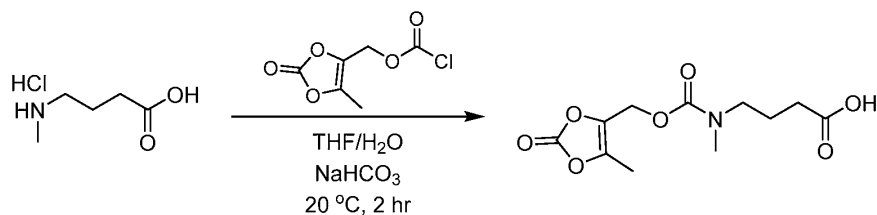
Example 7

Preparation of 4-(methylamino)butanoic acid



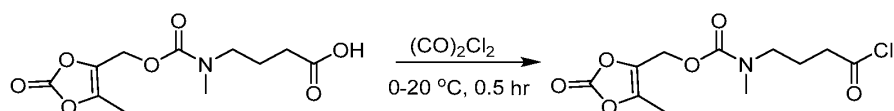
[000221] A mixture of 1-methylpyrrolidin-2-one (5.0 g, 50.44 mmol, 4.90 mL, 1 *eq*), HCl (51.0 g, 531.53 mmol, 50 mL, 38% purity, 10.54 *eq*) was stirred at 165 °C for 16 hr. The reaction mixture concentrated. The resulting residue was triturated from acetone to give 4-(methylamino)butanoic acid (4 g, 51.6% yield, HCl salt) as a white solid.

Preparation of 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoic acid



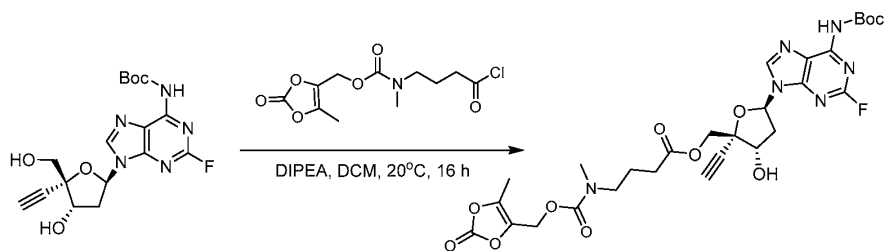
[000222] To a solution of 4-(methylamino)butanoic acid HCl salt (1.36 g, 8.83 mmol, 1 *eq*) in H₂O (25 mL) was added NaHCO₃ (2.23 g, 26.49 mmol, 1.03 mL, 3 *eq*) followed by (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonochloridate (1.7 g, 8.83 mmol, 1 *eq*) in THF (25 mL). The mixture was stirred at 20 °C for 16 hr. The reaction mixture was concentrated and purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~5% methanol/dichloromethane @ 20 mL/min) to give 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoic acid (1.5 g, 62.2% yield) as a colorless oil. ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm) 12.07 (br s, 1H), 4.89 (s, 2H), 3.22 (br t, *J*=7.2 Hz, 2H), 2.81 (s, 3H), 2.28 - 2.03 (m, 5H), 1.69 (m, 2H).

Preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl N-(4-chloro-4-oxo-butyl)-N-methyl-carbamate



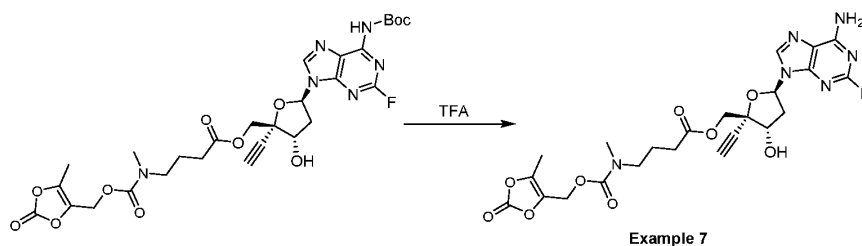
[000223] To a solution of 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoic acid (70 mg, 0.256 mmol, 1 *eq*) in DCM (5 mL) at 0°C was added DMF (0.2 mg, 0.0026 mmol, 0.01 *eq*) and oxalyl chloride (65 mg, 0.512 mmol, 0.045 mL, 2 *eq*). The mixture was stirred at 20°C for 0.5 hr. The reaction was concentrated to dryness to give (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl N-(4-chloro-4-oxo-butyl)-N-methyl-carbamate (50 mg, crude) as a yellow oil, which was used for next reaction without further purification.

Preparation of [(2R,3S,5R)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate



[000224] To a solution of *tert*-butyl *N*-[9-[(2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]carbamate (20 mg, 0.0508 mmol, 1 *eq*) in pyridine (2 mL) was added (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl-(4-chloro-4-oxo-butyl)-*N*-methyl-carbamate (66 mg, 0.226 mmol, 4.45 *eq*). The mixture was stirred at 20 °C for 16 hr. The reaction was concentrated to give [(2*R*,3*S*,5*R*)-5-[6-(*tert*-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate (35 mg, crude) as a yellow oil, which was used for next reaction without further purification.

Preparation of ((2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-9*H*-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl 4-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)butanoate



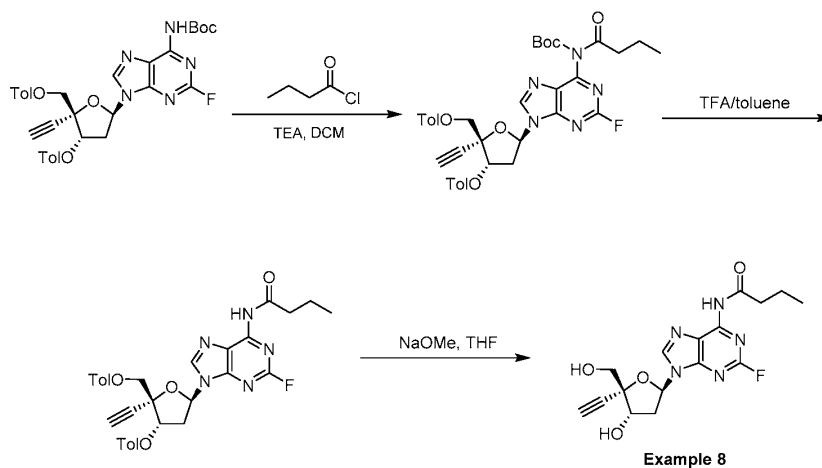
Example 7

[000225] To a solution of [(2*R*,3*S*,5*R*)-5-[6-(*tert*-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate (25 mg, 0.0386 mmol, 1 *eq*) in toluene (2 mL) was added TFA (770 mg, 0.675 mmol, 0.50 mL, 10%, 17.52 *eq*). The mixture was stirred at 20 °C for 16 hr and then concentrated to dryness.

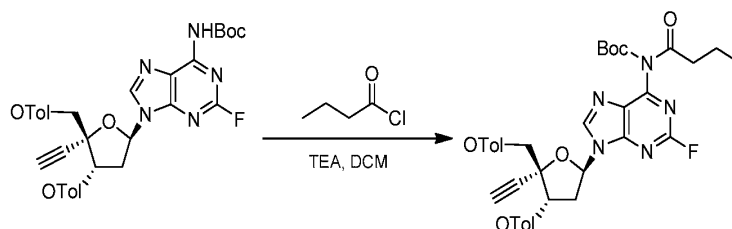
The residue was purified by prep-HPLC (TFA condition; column: Boston Green ODS 150*30mm*5um; mobile phase: [water(0.075%TFA)-ACN];B%: 20%-50%,12min) to give ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl 4-(methyl(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)butanoate (1.8 mg, 8.51% yield) was obtained as a light yellow solid. LCMS (ESI) m/z, C₂₃H₂₆FN₆O₉, calculated 548.2, found (M+H)⁺: 549.2. ¹H NMR (400MHz, CD₃OD) δ (ppm) 8.14 (s, 1H), 6.29 (m, 1H), 4.88 (s, 2H), 4.44 (t, J=11.2 Hz, 1H), 4.25 (t, J=11.2 Hz, 1H), 3.26 - 3.13 (m, 3H), 2.96 - 2.86 (m, 2H), 2.82 (s, 2H), 2.64 (m, 1H), 2.25 (m, 2H), 2.16 - 2.07 (m, 3H), 1.74 (m, 2H), 1.31 (s, 1H). ¹⁹F NMR (376MHz, CD₃OD) δ (ppm) -52.82 (s).

Example 8:

N-9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)butyramide

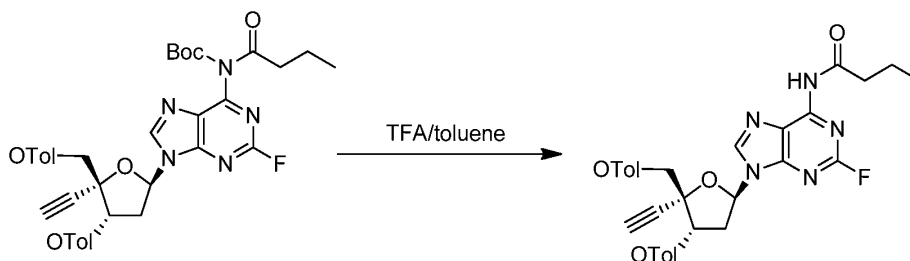


[000226] Preparation of [(2R,3S,5R)-5-[6-[butanoyl(tert-butoxycarbonyl)amino]-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000227] To a solution of [(2R,3S,5R)-5-[6-(tert-butoxycarbonylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (74 mg, 0.118 mmol, 1 *eq*) in DCM (5 mL) was added DMAP (1.5 mg, 0.012 mmol, 0.1 *eq*), TEA (36 mg, 0.354 mmol, 3.0 *eq*) and butanoyl chloride (25 mg, 0.235 mmol, 2 *eq*). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated and diluted with H₂O (30 mL), then extracted with EtOAc (15x3 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent of 0~20% ethyl acetate/petroleum ether gradient @18 mL/min) to give [(2R,3S,5R)-5-[6-[butanoyl(tert-butoxycarbonyl) amino]-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (30 mg, 30% yield) as light yellow oil. LCMS (ESI) *m/z*, C₃₇H₃₈FN₅O₈: calculated 700.3, found (M+H)⁺: 701.3.

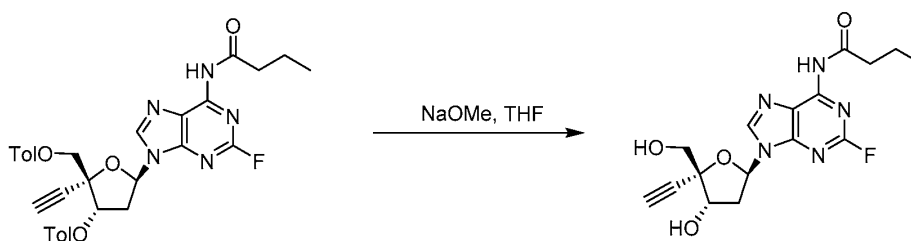
[000228] Preparation of [(2R,3S,5R)-5-[6-(butanoylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate



[000229] To a solution of [(2R,3S,5R)-5-[6-[butanoyl(tert-butoxycarbonyl)amino]-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (30 mg, 0.0428 mmol, 1 *eq*) in toluene

(1 mL) was added TFA (0.1 mL). The mixture was stirred at 25 °C for 16 h. The mixture was diluted with H₂O (2 mL) and extracted with EtOAc (3x3 mL), the combined organic layer was washed with brine (15x3 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 1:1) to give [(2R,3S,5R)-5-[6-(butanoylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyloxy)-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (18 mg, 64% yield) as an light yellow oil. LCMS (ESI) m/z, C₃₂H₃₀FN₅O₆: calculated 600.2, found (M+H)⁺: 601.3.

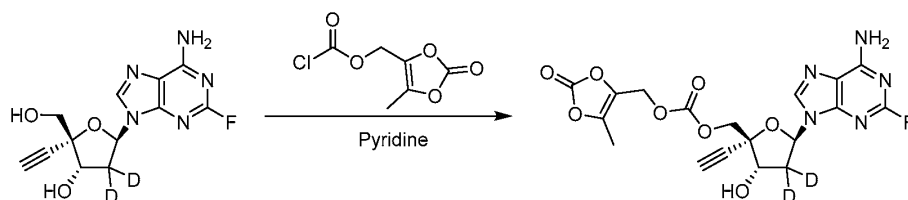
[000230] Preparation of N-[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]butanamide



[000231] To a solution of [(2R,3S,5R)-5-[6-(butanoylamino)-2-fluoro-purin-9-yl]-2-ethynyl-3-(4-methylbenzoyloxy)-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (18 mg, 0.030 mmol, 1 *eq*) in THF (2 mL) was added CH₃ONa (54 mg, 0.30 mmol, 30% purity in MeOH, 10 *eq*). The mixture was stirred at -25 °C for 4 h. The mixture was acidified with HOAc to pH = 7, then the mixture was concentrated. The resulting residue was purified by prep-HPLC (FA condition; column: 3_Phenomenex Luna C18 75x30mmx3um; mobile phase: [water (0.2%FA)-ACN]; B%: 15%~45%, 6 min) to give N-[9-[(2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-fluoro-purin-6-yl]butanamide (4.4 mg, 40% yield) as a white solid. LCMS (ESI) m/z, C₁₆H₁₈FN₅O₄: calculated 364.1, found (M+H)⁺: 365.2. ¹H NMR (400 MHz, CD₃CN) δ (ppm) 9.15 (bs, 1H), 8.26 (s, 1H), 6.37-6.34 (m, 1H), 4.70 (t, *J* = 6.4 Hz, 1H), 3.82-3.78 (m, 1H), 3.74-3.69 (m, 1H), 2.96-2.93 (m, 1H), 2.84-2.75 (m, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.59-2.52 (m, 2H), 1.74-1.67 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H). ¹⁹F NMR (376 MHz, CD₃CN) δ (ppm) -51.9 (s, 1F).

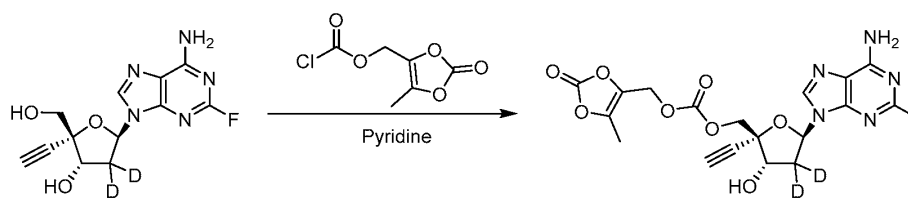
Example 9:

[(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate



Example 9

[000232] Preparation of [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate

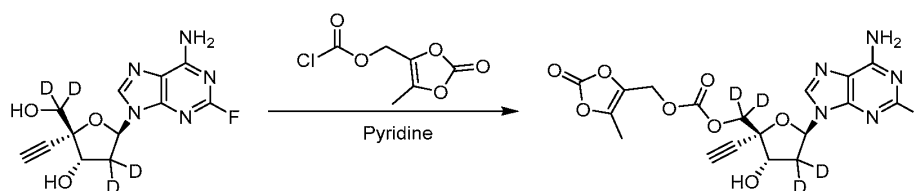


Example 9

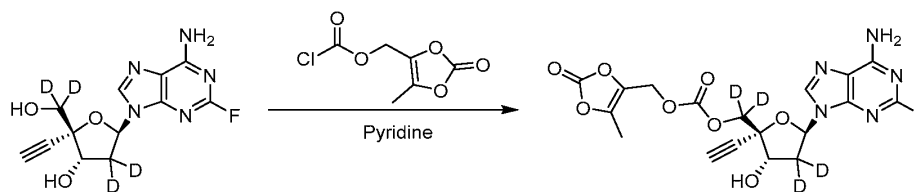
[000233] To a mixture of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (60 mg, 0.203 mmol, 1 *eq*) in pyridine (0.5 mL) was dropwise added (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonochloridate (195 mg, 1.02 mmol, 5 *eq*) in DCM (0.5 mL). The resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent with 0~5% methanol/dichloromethane gradient @ 18 mL/min) to give [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (21 mg, 22.9% yield) as a white solid. LCMS (ESI) *m/z*, C₁₈H₁₄D₂FN₅O₈: calculated 451.11 found (M+H)⁺: 452.1. ¹H NMR (400MHz, CD₃CN) δ (ppm) 7.92 (s, 1H), 6.31 (s, 2H), 6.25 (s, 1H), 4.9-4.82 (m, 2H), 4.73-4.71(d, *J* = 8 Hz, 1H), 4.52-4.50 (d, *J* = 8 Hz, 1H), 4.32-4.29 (d, *J* = 12 Hz, 1H), 3.74-3.72 (d, *J* = 8 Hz, 1H), 3.00 (s, 1H), 2.10 (s, 3H). ¹⁹F NMR (376MHz, CD₃CN) δ (ppm) -52.84 (s, 1F).

Example 10:

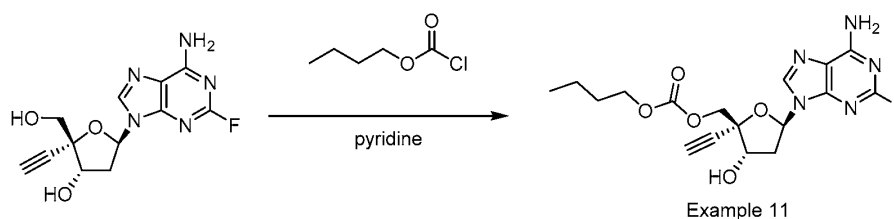
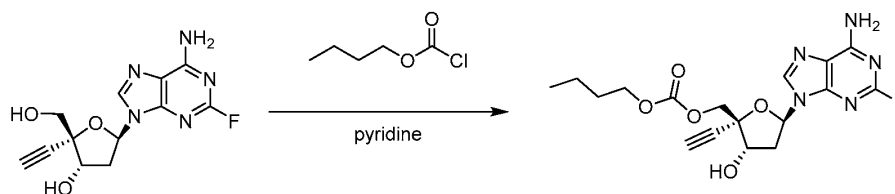
[[[(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]-dideuterio-methyl] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate

**Example 10**

[000234] Preparation of [[[(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]-dideuterio-methyl] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate

**Example 10**

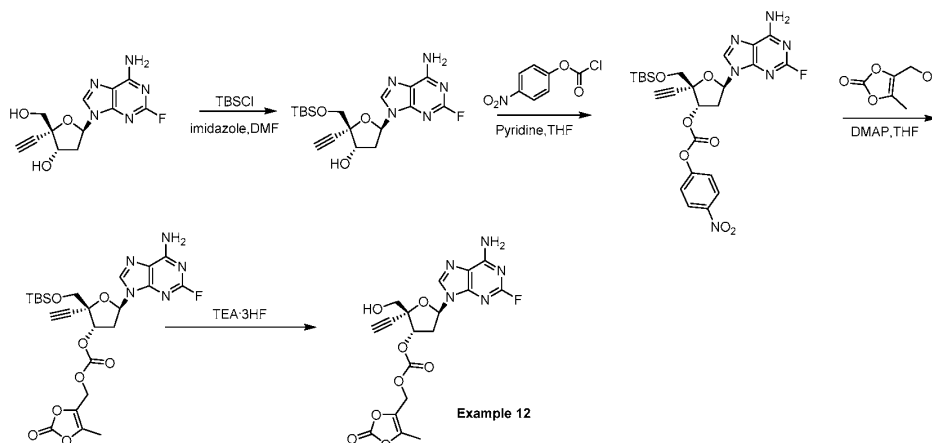
[000235] To a mixture of (2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-[dideuterio(hydroxy)methyl]-2-ethynyl-tetrahydrofuran-3-ol (50 mg, 0.168 mmol, 1 *eq*) in pyridine (0.5 mL) was dropwise added (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonochloridate (162 mg, 0.84 mmol, 5 *eq*) in DCM (0.5 mL). The resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent with 0~5% methanol/dichloromethane gradient @ 18 mL/min) to give [[[(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-4,4-dideuterio-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]-dideuterio-methyl] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (40.6 mg, 53% yield) as a white solid. LCMS (ESI) *m/z*, C₁₈H₁₂D₄FN₅O₈: calculated 453.3, found (M+H)⁺: 454.2. ¹H NMR (400MHz, DMSO-d₆) δ (ppm) 7.92 (s, 1H), 6.31 (s, 2H), 6.25 (s, 1H), 4.91-4.82 (m, 2H), 4.72-4.71(d, *J* = 4 Hz, 1H), 3.74-3.72(d, *J* = 8 Hz, 1H), 3.00 (s, 1H), 2.10 (s, 3H). ¹⁹F NMR (376MHz, DMSO-d₆) δ (ppm) -52.85 (s, 1F).

Example 11:**((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl butyl carbonate****[000236] Preparation of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl butyl carbonate**

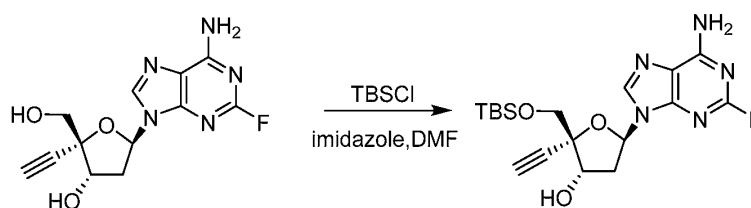
[000237] To a solution of ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (50 mg, 0.17 mmol, 1 eq) in pyridine (0.5 mL) was added butyl carbonochloridate (26 mg, 0.187 mmol, 0.024 mL, 1.1 eq) slowly at 0 °C and stirred the mixture for 2 h. The reaction mixture was concentrated, the resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluted with 0~5% MeOH/DCM @ 30 mL/min) to give compound ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl butyl carbonate (7.6 mg, 11.3% yield) as a white solid. LCMS (ESI) m/z , $C_{17}H_{20}FN_5O_5$: calculated 393.14, found $(M+H)^+$: 394.1. 1H NMR (400MHz, CD_3CN) δ (ppm): 7.96 (s, 1H), 6.27 (m, 3H), 4.73 (q, $J = 6.8$ Hz, 1H), 4.46 (d, $J = 11.6$ Hz, 1H), 4.31-4.23 (m, 1H), 4.10-3.99 (m, 2H), 3.75-3.66 (m, 1H), 2.99 (s, 1H), 2.85 (m, 1H), 2.57 (m, 1H), 1.61-1.52 (m, 2H), 1.28 (m, 2H), 0.94-0.87 (m, 3H); ^{19}F NMR (376MHz, CD_3CN) δ (ppm): -52.86 (s, 1F).

Example 12:

(2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-yl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate



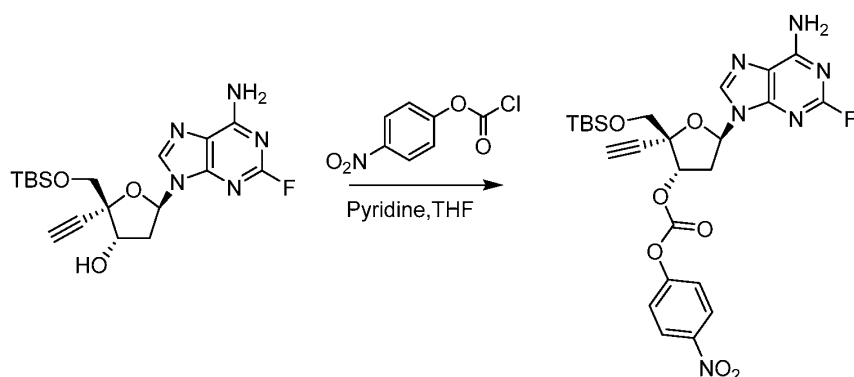
[000238] Preparation of (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-ethynyltetrahydrofuran-3-ol



[000239] To a solution of (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (0.5 g, 1.71 mmol, 1 eq) in DMF (5 mL) was added imidazole (349 mg, 5.13 mmol, 3 eq) and TBSCl (386 mg, 2.56 mmol, 1.5 eq). The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluted with 0~5% MeOH/DCM @ 18 mL/min) to give (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-ethynyltetrahydrofuran-3-ol (331 mg, 47.5% yield) as a light yellow solid. ¹H NMR (400MHz, CD₃CN) δ (ppm) 8.03 (s, 1H), 6.39-6.17 (m, 3H), 4.71 (q, *J* = 6.8 Hz, 1H), 3.93-3.87 (m, 1H), 3.84-3.76 (m, 1H), 3.49 (d, *J* =

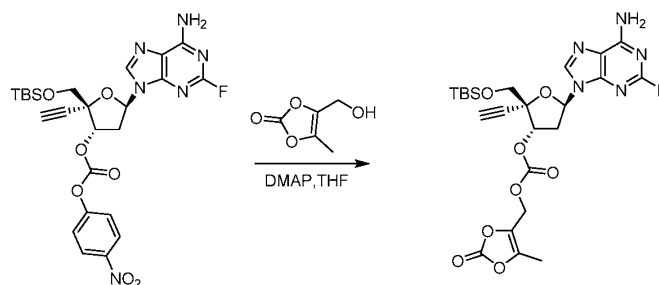
6.4 Hz, 1H), 2.91 (s, 1H), 2.85-2.73 (m, 1H), 2.55 (m, 1H), 2.50 (s, 2H), 0.88-0.82 (m, 9H), 0.02 (d, $J = 16$ Hz, 6H); ^{19}F NMR (376MHz, CD_3CN) δ (ppm) -53.04 (s, 1F).

[000240] Preparation of [(2R, 3S, 5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-[[tert-butyl (dimethyl) silyl]oxymethyl]-2-ethynyl-tetrahydrofuran-3-yl] (4-nitrophenyl) carbonate



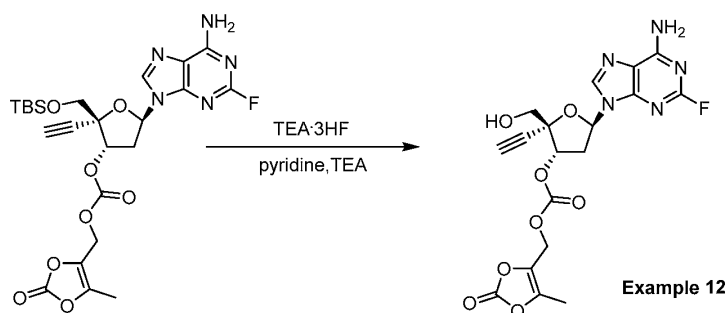
[000241] To a solution of (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-(((tert-butyl dimethylsilyl)oxy)methyl)-2-ethynyltetrahydrofuran-3-ol (100 mg, 0.245 mmol, 1 eq) in THF (2 mL) was added pyridine (0.40 mL, 20 eq) and (4-nitrophenyl) carbonochloridate (494 mg, 2.45 mmol, 10 eq). The mixture was stirred at 25 °C for 50 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluted with 0~5% MeOH/DCM@ 18 mL/min) to give compound [(2R, 3S, 5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-[[tert-butyl (dimethyl) silyl]oxymethyl]-2-ethynyl-tetrahydrofuran-3-yl] (4-nitrophenyl) carbonate (178 mg, crude) as a light yellow solid.

[000242] Preparation of [(2R, 3S, 5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-[[tert-butyl (dimethyl) silyl]oxymethyl]-2-ethynyl-tetrahydrofuran-3-yl] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate



[000243] To a solution of [(2R, 3S, 5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-[[tert-butyl (dimethyl) silyl]oxymethyl]-2-ethynyl-tetrahydrofuran-3-yl] (4-nitrophenyl) carbonate (249 mg, 0.435 mmol, 1 eq) in THF (4 mL) was added DMAP (5 mg, 0.043 mmol, 0.1 eq) and 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (170 mg, 1.30 mmol, 3 eq). The mixture was stirred at 30 °C for 2 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluted with 0~5% MeOH/DCM@ 18 mL/min) to give compound [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-ethynyl-tetrahydrofuran-3-yl] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (239 mg, 97.6% yield) as a brown solid. ¹H NMR (400MHz, CD₃CN) δ (ppm): 8.06-7.95 (m, 1H), 6.42-6.26 (m, 3H), 5.61 (m, 1H), 4.97 (m, 2H), 3.98-3.93 (m, 1H), 3.89-3.83 (m, 1H), 3.16-3.03 (m, 1H), 2.95 (s, 1H), 2.70 (m, 1H), 2.15 (s, 3H), 0.86 (s, 9H), 0.04 (d, *J* = 10.3 Hz, 6H); ¹⁹F NMR (376MHz, CD₃CN) δ (ppm): -52.66 (s, 1F).

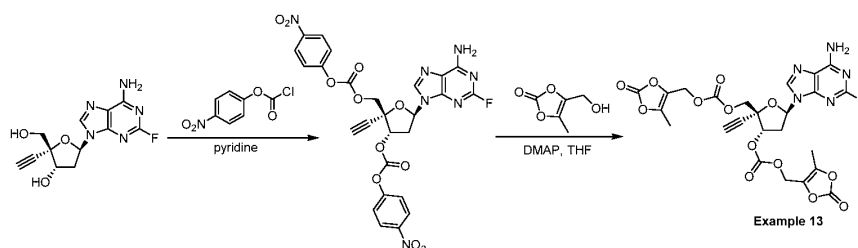
[000244] Preparation of (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-yl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate



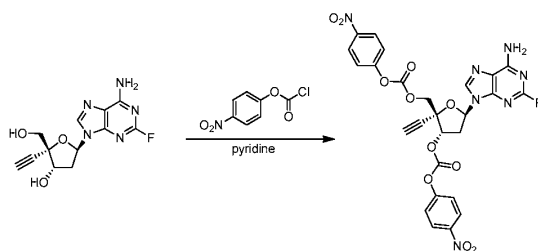
[000245] To a solution of [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-ethynyl-tetrahydrofuran-3-yl] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (359 mg, 0.637 mmol, 1 eq) in pyridine (3.5 mL) and TEA (3.5 mL) was added *N,N*-diethylethanamine; trihydrofluoride (3.55 g, 22.02 mmol, 34.58 eq) at 0 °C, then the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluted with 0~5% MeOH/DCM @ 18 mL/min) to give (2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-9*H*-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-yl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate (230 mg, 80% yield) as a white solid. LCMS (ESI) *m/z*, C₁₈H₁₆FN₅O₈: 449.1, found (M+H)⁺: 450.1. ¹H NMR (400MHz, CD₃CN) δ(ppm): 7.95 (s, 1H), 6.47 (s, 2H), 6.34 (m, 1H), 5.53 (m, 1H), 5.02-4.93 (m, 3H), 3.92-3.70 (m, 2H), 3.07 (m, 1H), 2.95 (s, 1H), 2.61 (m, 1H), 2.15 (s, 3H); ¹⁹F NMR (376MHz, CD₃CN) δ (ppm): -53.27 (s, 1F).

Example 13:

((2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-9*H*-purin-9-yl)-2-ethynyl-3-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyloxy)tetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate

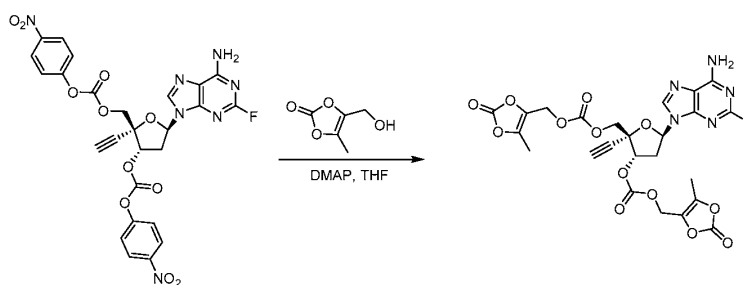


[000246] Preparation of [(2*R*,3*S*,5*R*)-5-(6-Amino-2-fluoro-purin-9-yl)-2-ethynyl-2-[(4-nitrophenoxy)carbonyloxymethyl]tetrahydrofuran-3-yl] (4-nitrophenyl) carbonate



[000247] To a solution of (2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (100 mg, 0.341 mmol, 1 *eq*) in DCM (5 mL) was added pyridine (674 mg, 8.53 mmol, 25 *eq*) and (4-nitrophenyl) carbonochloridate (1.03 g, 5.12 mmol, 15 *eq*) at 26 °C. The mixture was stirred at 26 °C for 4 hr. The mixture was quenched with H₂O (30 mL). The mixture was added DCM (30 mL) and washed with H₂O (30 mL), brine (30 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~6 % Methanol/Dichloromethane gradient @ 18 mL/min) to give [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-[(4-nitrophenoxy)carbonyloxymethyl]tetrahydrofuran-3-yl] (4-nitrophenyl) carbonate (137 mg, 51% yield, 80% purity) as a white solid. LCMS (ESI) *m/z*, C₂₆H₁₈FN₇O₁₁: calculated 623.10, found 624.1 (M+H)⁺.

[000248] Preparation of [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyloxymethyl]tetrahydrofuran-3-yl] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate



[000249] To a solution of [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-[(4-nitrophenoxy)carbonyloxymethyl]tetrahydrofuran-3-yl] (4-nitrophenyl) carbonate (99 mg, 0.159 mmol, 1 *eq*) in THF (5 mL) was added DMAP (1.9 mg, 0.016

mmol, 0.1 *eq*) and 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (248 mg, 1.91 mmol, 12 *eq*). The mixture was stirred at 25 °C for 16 h. The mixture was quenched with H₂O (30 mL). The mixture was added DCM (30 mL). The mixture was washed with H₂O (30 mL) and brine (30 mL). The organic layer was dried over Na₂SO₄ and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10 % Methanol/Dichloromethane gradient @ 18 mL/min) to give [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyloxymethyl]tetrahydrofuran-3-yl][(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate (89 mg, 56% yield, 60% purity). The material was further purified with flash silica gel chromatography and recrystallized (CH₃CN/Hep) to provide [(2*R*,3*S*,5*R*)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-2-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyloxymethyl]tetrahydrofuran-3-yl][(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl carbonate as a white solid. LCMS (ESI) *m/z*, C₂₄H₂₀FN₅O₁₃: calculated 605.10, found (M+H)⁺: 606.1. ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm) 8.30 (s, 1H), 7.89 (br s, 2H), 6.38-6.34 (m, 1H), 5.62-5.59 (m, 1H), 5.14-5.06 (m, 2H), 4.99 (s, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 3.83 (s, 1H), 3.21-3.17 (m, 1H), 2.73-2.70 (m, 1H), 2.19 (s, 3H), 2.14 (s, 3H). ¹⁹F NMR (376MHz, DMSO-*d*₆) δ (ppm) -51.47 (s, 1F).

Example 14:

Conversion and Stability of the Adenosine Derivative Prodrugs

[000250] Stability of prodrugs and conversion of the prodrugs to the parent EFdA (formula T-1A) were measured in both plasma and liver S9 assays and the data are shown in **Table 2**.

Plasma stability

[000251] The pooled frozen plasma was thawed in a water bath at 37°C prior to experiment. Plasma was centrifuged at 4000 rpm for 5 min and the clots were removed if any. The pH will be adjusted to 7.4 ± 0.1 if required.

Preparation of test compounds and positive control (propantheline bromide): 1 mM intermediate solution was prepared by diluting 10 µL of the stock solution with 90 µL MeOH; 1 mM intermediate of positive control Propantheline was prepared by diluting 10 µL of the stock solution with 90 µL ultrapure water. 100 µM dosing solution was

prepared by diluting 20 μ L of the intermediate solution (1 mM) with 180 μ L MeOH. 98 μ L of blank plasma was spiked with 2 μ L of dosing solution (100 μ M) to achieve 2 μ M of the final concentration in duplicate and samples were incubated at 37°C in a water bath. At each time point (0, 10, 30, 60 and 120 min), 400 μ L of stop solution (0.1% FA in MeOH containing 200 ng/mL tolbutamide and 200 ng/mL Labetalol) was added to precipitate protein and mixed thoroughly. Centrifuged sample plates at 4,000 rpm for 10 min. An aliquot of supernatant (100 μ L) was transferred from each well to another plates.

Data analysis: The % remaining of test compound after incubation in plasma was calculated using following equation:

$$\% \text{ Remaining} = 100 \times (\text{PAR at appointed incubation time} / \text{PAR at T0 time})$$

where PAR is the peak area ratio of analyte versus internal standard (IS) (LC/MS/MS mobile phase condition: 0.1% Formic Acid in Water / 0.1% Formic Acid in Acetonitrile). The appointed incubation time points are T0 (0 min), Tn (n=0, 10, 30, 60, 120 min).

Liver S9 stability

[000252] Intermediate solution: Dilute 5 μ L of compounds or controls (7-ethoxycoumarin) from stock solution (10 mM) with 495 μ L MeOH (Conc.: 100 μ M, 1%DMSO, 99%MeOH). Stop solution: Cold ACN (including 100 ng/mL Tolbutamide and Labetalol as internal standard). Add 2 μ L test compound or control working solution/well to all plates (T0, T5, T10, T20, T30, T60, NCF60) except matrix blank. Add 600 μ L/well stop solution (cold in 4°C, including 100 ng/mL Tolbutamide/ 100 ng/mL Labetalol) to terminate the T0 plate, then put it on ice. Dispense 840 μ L/well S9 solution to 96-well plate as reservoir according to plate map. Then add 100 μ L/well to every plate by Apricot. Incubate S9 solution and compound at 37°C for about 10 min except NCF60 and T0. After adding S9 solution and 98 μ LPB buffer to NCF60, incubate at 37°C without pre-warming, start timer 1. After 60 min, add 600 μ L/well stop solution to terminate the reaction. After pre-warming, dispense 760 μ L/well cofactor solution to 96-well plate as reservoir according to plate map. Then add 98 μ L/well to every plate by Apricot to start reaction. Incubate at 37°C, start timer 2, Add 600 μ L/well stop solution (cold in 4°C, including 100 ng/mL Tolbutamide and Labetalol) to terminate the reaction. Samples are centrifuged at 4000 rpm for 20 min. While centrifuging, load 8×new 96-well plate with 300 μ L HPLC water, then transfer 100 μ L supernatant, mix with water for LC/MS/MS, transferred to Bioanalytical

Services for LC-MS/MS analysis. Use equation of first order kinetics to calculate $t_{1/2}$ and CL: Equation of first order kinetics:

$$C_t = C_0 \cdot e^{-k_e \cdot t}$$

$$C_t = \frac{1}{2} C_0, T_{1/2} = \frac{\ln 2}{-k_e} = \frac{0.693}{-k_e}$$

$$CL_{int(S9)} = Vd \cdot k_e$$

$$Vd = 1 \text{ mL/mg}$$

The stability results of exemplary compounds in human plasma and human liver S9 were listed in **Table 2** below.

Table 2. Conversion and Half Life Data.

Formula	Stability in Human Plasma		Stability in Human Liver S9	
	Half-life	Formation of EFdA	Half-life	Formation of EFdA
2-A	A	No	B	No
3-A	A	No	B	No
4-A	C	Yes	C	Yes
5-A	A	No	B	No
6-A	C	No	C	Yes
7-A	B	No	C	No
4-C	C	Yes	C	Yes

Half-life ranges: A : >200 minutes; B: 50-200 minutes; C: < 50 minutes.

[000253] Data showed that adenosine derivative 4-A and 4-C can be converted to the target drug efficiently in human plasma and liver S9 assays, and 6-A can be converted to the target drug efficiently in liver S9 assay.

Example 15:

Plasma Exposures Following Oral Administration of Prodrugs to Beagle Dogs

[000254] The pharmacokinetics of EFdA and prodrug formula 4-A were studied in dogs after oral administration of a 5 mg-equivalent/kg EFdA dose.

[000255] **Formulations:** The prodrugs were formulated as solutions at 1.65 mg/mL in 20% PEG400 aqueous solution within 0.5 hour prior to dose.

[000256] **Dose Administration and Sample Collection:** The in-life phase of this study was conducted at the Charles River Laboratory (CRL) at Worcester, MA in

accordance with the CRL Institutional Animal Care and Use Committee (IACUC) standard animal procedures along with the IACUC guidelines that are in compliance with the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals, and was approved by the IACUA Committee. Fasted male beagle dogs (10 +/- 2 kg) were used for the studies. Each drug was administered as a single dose by oral gavage (5 ml/kg). The prodrug formula 4-A dose (8.25 mg/kg) was dose-equivalent to 5 mg/kg of EFdA. Plasma samples were collected at 0 (pre-dose), 30 min, 1, 2, 4, 6, 8, 12 and 24 h post-dose. Blood (approximately 0.1 to 0.2 mL) was processed immediately for plasma by centrifugation at 3,500 rpm at 5°C for 10 min immediately after collection. Plasma samples were frozen and maintained at -70°C until analyzed. To stabilize the prodrug at the sample collection and subsequent analysis, the following stabilizing reagents were added to the blood collection K2EDTA tubes on wet ice prior to sample collection: for each 100 mL of blood, 15 mL of premade inhibitor cocktail consists of 1 mM DFP, 100 mM dichlorvos, 100 mM 2-Hydroxyquinoline, 100 mM PCMB, 1 mM Paraoxon, 100 mM PMSF, 100 mM NaF, 30.0 mM EDTA, and 15 mM Citric Acid, 10 mL of 0.2M eserine, and 10 mL of 0.2M BNPP solutions.

[000257] Determination of EFdA and Prodrugs in plasma: Briefly, plasma (20 µL) was mixed with 100 µL acetonitrile to precipitate protein. Consistent with sample collection procedure, the same cocktail protocol was also added to stabilize the prodrug in the standard and QC samples.

[000258] Bioanalysis: A Sciex API-6500 triplequadrupole mass spectrometer coupled with a Shimadzu HPLC system (Framingham, MA 01701) was used for quantitative analysis of plasma samples. The column was a Waters HSS T3 column (2.1 x 50 mm, 1.8mm). The mobile phases used were: A, 5% acetonitrile in 2 mM ammonium formate buffer; B, 95% acetonitrile in 2 mM ammonium formate buffer, pH 6.0. The flow rate was 0.6 mL/min with a total run time of 3.0 min. The HPLC gradient was initiated at 98% A/2% B for 0.20 min, followed by linear gradient increase to 25% over the next 1.40 min; the gradient was subsequently increased to 100% of mobile B over the next 1.0 min and then held for additional 0.2 min before ramping down to 2% mobile phase B within the following 0.2 min. Detection of the prodrug and EFdA were achieved using positive ion electrospray mass spectroscopic mode using unit resolution mode. Multiple reaction monitoring (MRM) modes were used to quantify both prodrug and EFdA, e.g. the MRM transition for EFdA was 294.0-153.90 Da, and the transition for prodrug 4-A was 450.0-153.9 Da. Peak areas were integrated

by the Sciex program Analyst®, version 1.6.3, operating on a Windows 7 computer where concentrations were determined by a weighted (1/x²) linear regression of peak area ratios (peak area of EFdA/peak area of corresponding IS) versus the nominal concentrations of the plasma calibration standards. Calculations were performed on unrounded numbers. Overall, Analyst® determined the precision and accuracy for the calibration standards and QC samples.

[000259] Pharmacokinetic Calculations: The noncompartmental (NCA) analysis of EFdA and prodrug individual plasma concentration-time data were conducted using WinNonlin module in the Phoenix PK/PD Platform (version 8.3.0.5005, Certara Inc., Princeton, NJ 08540). Calculations were performed prior to rounding and nominal sampling times were used in the pharmacokinetic analysis. Exposures were expressed as areas under concentration curves in plasma from zero to 24 hours (AUC_{0-24h}). The AUC values were calculated using the linear trapezoidal rule.

[000260] Plasma Concentrations: The results of the PK studies are shown in Tables 3 and 4. These data establish *in vivo* that prodrug formula 4-A can be readily delivered orally, and can efficiently release EFdA *in vivo* with minimal prodrug detected in the systemic circulation. For example, prodrug formula 4-A can release significantly more EFdA *in vivo* than a dose-equivalent EFdA, i.e., 91%, 102%, 55%, 79%, and 200% more at 0.25, 0.5, 1, 2, and 4-hour time points (see Table 3). Further, prodrug formula 4-A can produce a higher AUC and C_{max} than a dose-equivalent EFdA (see Table 4).

Table 3: Plasma concentration of EFdA and prodrug formula 4-A after a single oral dose to male beagle dogs

EFdA Concentrations (ng/mL) in Dog Plasma						
Prodrug formula 4-A PO (8.25 mg/kg)	Animal ID					
Time Points (hrs)	2001	2002	2003	Mean	SD	%CV
0.250	463	533	1040	679	315	46.4%
0.500	593	621	749	654	83.2	12.7%
1.00	585	555	538	559	23.8	4.3%
2.00	369	410	239	339	89.3	26.3%
4.00	33.4	45.4	31.9	36.9	7.40	20.1%
6.00	4.93	5.39	2.45	4.26	1.58	37.1%
8.00	1.30	1.84	1.76	1.63	0.291	17.9%
12.0	BQL	BQL	BQL	NA	NA	NA
24.0	BQL	BQL	BQL	NA	NA	NA
Prodrug formula 4-A Concentrations (ng/mL) in Dog Plasma						
Prodrug formula 4-A PO (8.25 mg/kg)	Animal ID					
Time Points (hrs)	2001	2002	2003	Mean	SD	%CV
0.250	1.13	1.63	1.09	1.28	0.301	23.5%
0.500	BQL	1.68	BQL	1.68	NA	NA
1.00	BQL	BQL	1.43	1.43	NA	NA
2.00	BQL	BQL	BQL	NA	NA	NA
4.00	BQL	BQL	BQL	NA	NA	NA
6.00	BQL	BQL	BQL	NA	NA	NA
8.00	BQL	BQL	BQL	NA	NA	NA
12.0	BQL	BQL	BQL	NA	NA	NA
24.0	BQL	BQL	BQL	NA	NA	NA
EFdA Concentrations (ng/mL) in Dog Plasma						
EFdA PO (5 mg/kg)	Animal ID					
Time Points (hrs)	4001	4002	4003	Mean	SD	%CV
0.250	456	333	276	355	92.0	25.9%
0.500	391	299	280	323	59.4	18.4%
1.00	369	353	361	361	8.00	2.2%
2.00	211	212	143	189	39.6	21.0%
4.00	12.6	17.9	6.30	12.3	5.81	47.2%
6.00	BQL	BQL	BQL	NA	NA	NA
8.00	BQL	BQL	BQL	NA	NA	NA
12.0	BQL	BQL	BQL	NA	NA	NA
24.0	BQL	BQL	BQL	NA	NA	NA

BQL=below quantitation level; NA=not applicable

Table 4: EFdA Exposure in Plasma from Oral Administration of EFdA and Prodrug formula 4-A in Dogs

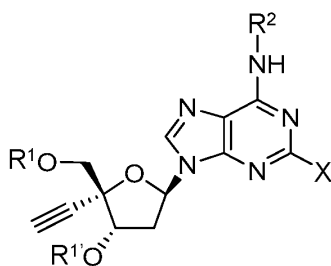
Compound	Dose (mg/kg)	AUC (ng*hr/mL)	C _{max} (ng/mL)
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EFdA	5	792	392
Prodrug formula 4-A	8.25 (~5 mg eq EFdA)	1432	753

Numbered Embodiments of the Disclosure

[000261] Other subject matter contemplated by the present disclosure is set out in the following numbered embodiments:

1. An adenosine derivative having a formula (1) or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof:

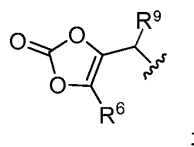


wherein,

R^1 , $R^{1'}$, and R^2 each is independently -H, -C(O)N(R^3)($R^{3'}$), -C(O)OR⁴, -R⁵, -L¹-R⁵, or -Z-L⁴-R⁵, wherein at least one of R^1 and R^2 is not -H;

R^3 , $R^{3'}$ and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

R^5 is:



R^6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

$-L^1-R^5$ is $-(C1-C10 \text{ alkyl})-N(R^7)-R^5$, $-(C1-C10 \text{ alkyl})-O-R^5$, $-(C1-C10 \text{ alkyl})-S-R^5$, $-(C2-C10 \text{ alkenyl})-N(R^7)-R^5$, $-(C2-C10 \text{ alkenyl})-O-R^5$, $-(C2-C10 \text{ alkenyl})-S-R^5$, $-C(O)O-R^5$, $-C(O)O-L^2-N(R^7)-R^5$, $-C(O)O-L^2-O-R^5$, $-C(O)O-L^2-S-R^5$, $-C(O)O-L^2-C(O)O-R^5$, $-C(O)O-L^2-C(O)N(R^7)-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-N(R^7)-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-O-R^5$, $-C(O)O-L^2-C(O)N(R^7)-L^3-S-R^5$, $-C(O)N(R^7)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)-R^5$, $-C(O)N(R^7)-L^2-O-R^5$, $-C(O)N(R^7)-L^2-S-R^5$, $-C(O)N(R^7)-L^2-C(O)O-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-N(R^7)-R^5$, $-C(O)O-L^2-N(R^7)C(O)O-R^5$, $-C(O)N(R^8)-L^2-N(R^7)C(O)O-R^5$, $-C(O)O-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-O-R^5$ or $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-S-R^5$;

$-Z-$ is a divalent $-C(O)-$, $-C(O)O-$, or $-C(O)N(R^7)-$;

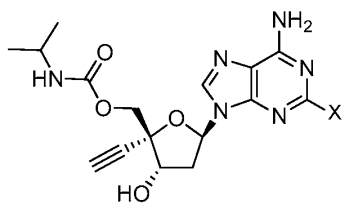
$-L^4-R^5$ is $-(C1-C10 \text{ alkyl})-N(R^7)-R^5$, $-(C1-C10 \text{ alkyl})-O-R^5$, $-(C1-C10 \text{ alkyl})-S-R^5$, $-(C2-C10 \text{ alkenyl})-N(R^7)-R^5$, $-(C2-C10 \text{ alkenyl})-O-R^5$ or $-(C2-C10 \text{ alkenyl})-S-R^5$;

R^7 , R^8 and R^9 each is independently $-H$, $C1-C10 \text{ alkyl}$, or $C2-C10 \text{ alkenyl}$;

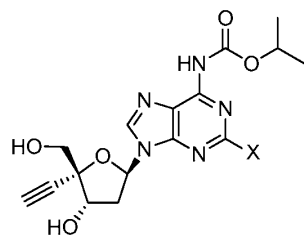
L^2 and L^3 each is intendedly divalent $-(C1-C10 \text{ alkyl})-$, or $-(C2-C10 \text{ alkenyl})-$; and

X is a halogen atom.

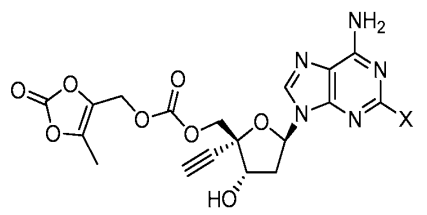
- The adenosine derivative of embodiment 1, wherein said adenosine derivative has a formula (2):



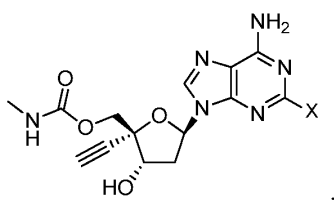
formula (3):



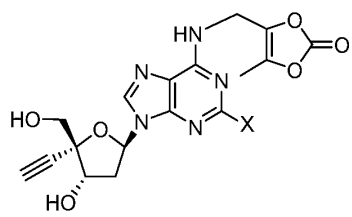
formula (4):



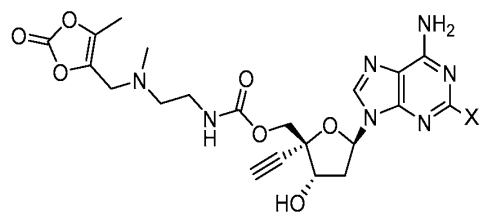
formula (5):



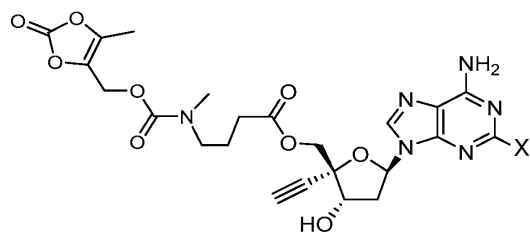
formula (6):



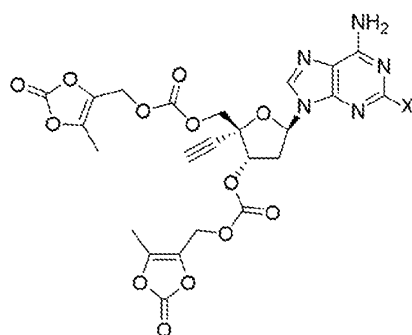
formula (7):



formula (8):

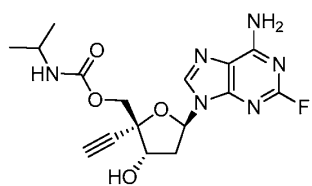


formula (4-B):

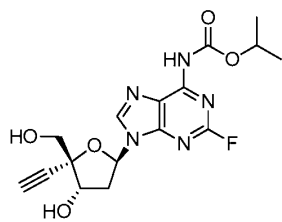


or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof.

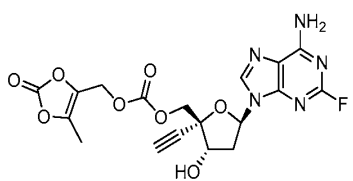
- The adenosine derivative of embodiment 1, wherein said adenosine derivative has a formula (2-A):



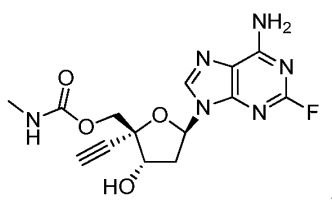
formula (3-A):



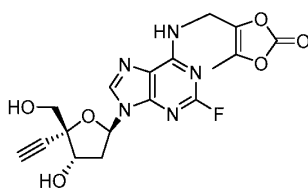
formula (4-A):



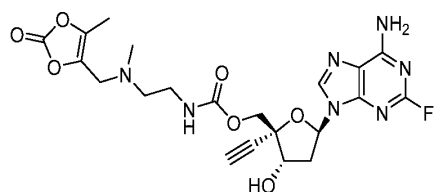
formula (5-A):



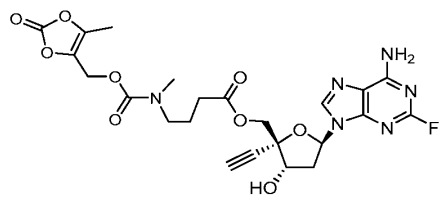
formula (6-A):



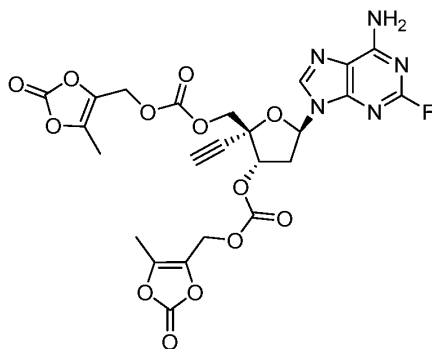
formula (7-A):



formula (8-A):



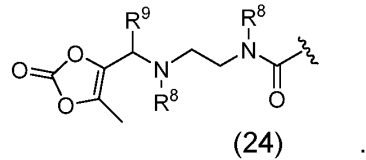
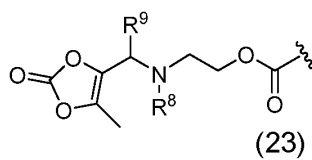
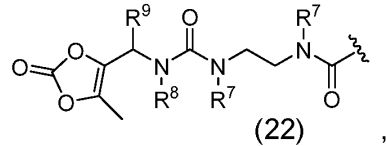
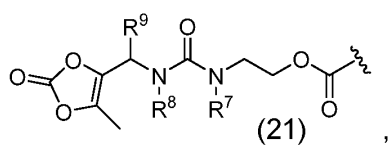
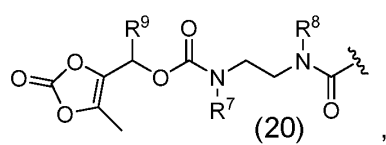
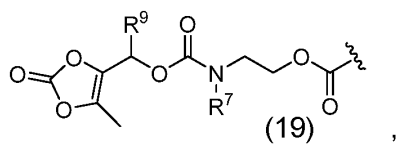
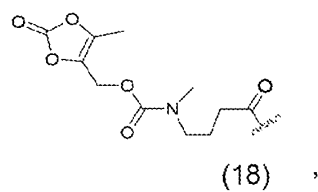
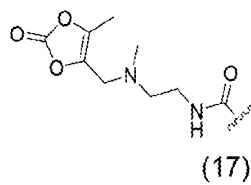
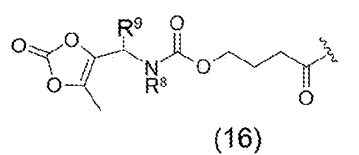
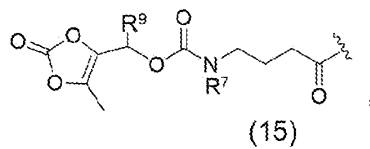
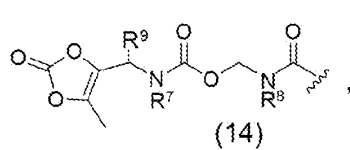
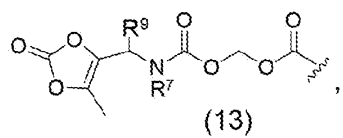
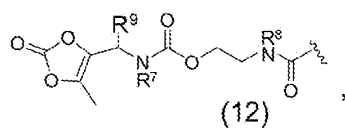
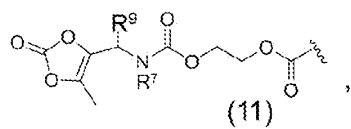
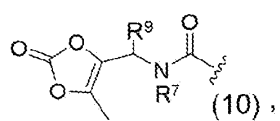
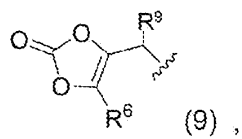
formula (4-C):



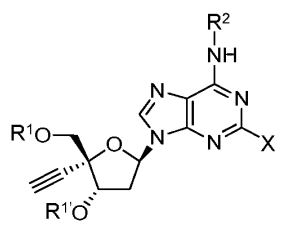
or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof.

4. The adenosine derivative of embodiment 1, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate.
5. The adenosine derivative of embodiment 1, wherein said adenosine derivative is isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate.
6. The adenosine derivative of embodiment 1, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate.
7. The adenosine derivative of embodiment 1, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate.

8. The adenosine derivative of embodiment 1, wherein said adenosine derivative is 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one.
9. The adenosine derivative of embodiment 1, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate.
10. The adenosine derivative of embodiment 1, wherein said adenosine derivative is [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate.
11. The adenosine derivative of embodiment 1, wherein said R^5 , $-L^1-R^5$ or $-Z-L^4-R^5$ is selected from formulas 9 – 24:



12. The adenosine derivative of any one of embodiments 1-11, wherein said adenosine derivative comprises a reverse transcriptase inhibitor activity in vivo, a reverse transcriptase chain terminator activity in vivo, DNA translocation inhibitor activity in vivo, or a combination thereof.
13. A pharmaceutical composition comprising an adenosine derivative having a formula (1):

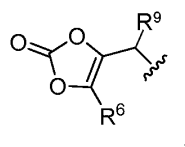


wherein,

R^1 , $R^{1'}$, and R^2 each is independently -H, -C(O)N(R^3)($R^{3'}$), -C(O)OR⁴, -R⁵, -L¹-R⁵, or -Z-L⁴-R⁵, wherein at least one of R^1 and R^2 is not -H;

R^3 , $R^{3'}$ and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

R^5 is:



R^6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

-L¹-R⁵ is -(C1-C10 alkyl)-N(R^7)-R⁵, -(C1-C10 alkyl)-O-R⁵, -(C1-C10 alkyl)-S-R⁵, -(C2-C10 alkenyl)-N(R^7)-R⁵, -(C2-C10 alkenyl)-O-R⁵, -(C2-C10 alkenyl)-S-R⁵, -C(O)O-R⁵, -C(O)O-L²-N(R^7)-R⁵, -C(O)O-L²-O-R⁵, -C(O)O-L²-S-R⁵, -C(O)O-L²-C(O)O-R⁵, -C(O)O-L²-C(O)N(R^7)-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-N(R^7)-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-O-R⁵, -C(O)O-L²-C(O)N(R^7)-L³-S-R⁵, -

$C(O)N(R^7)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)-R^5$, $-C(O)N(R^7)-L^2-O-R^5$, $-C(O)N(R^7)-L^2-S-R^5$, $-C(O)N(R^7)-L^2-C(O)O-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-N(R^7)-R^5$, $-C(O)O-L^2-N(R^7)C(O)O-R^5$, $-C(O)N(R^8)-L^2-N(R^7)C(O)O-R^5$, $-C(O)O-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-N(R^7)C(O)N(R^8)-R^5$, $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-O-R^5$ or $-C(O)N(R^7)-L^2-C(O)N(R^8)-L^3-S-R^5$;

-Z- is a divalent $-C(O)-$, $-C(O)O-$, or $-C(O)N(R^7)-$;

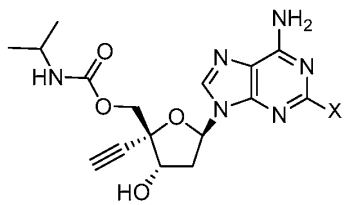
$-L^4-R^5$ is $-(C1-C10 \text{ alkyl})-N(R^7)-R^5$, $-(C1-C10 \text{ alkyl})-O-R^5$, $-(C1-C10 \text{ alkyl})-S-R^5$, $-(C2-C10 \text{ alkenyl})-N(R^7)-R^5$, $-(C2-C10 \text{ alkenyl})-O-R^5$ or $-(C2-C10 \text{ alkenyl})-S-R^5$;

R^7 , R^8 and R^9 each is independently $-H$, $C1-C10$ alkyl, or $C2-C10$ alkenyl;

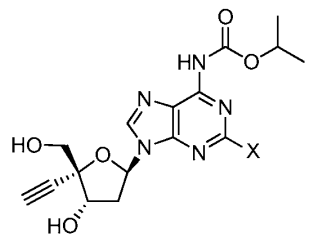
L^2 and L^3 each is intendedly divalent $-(C1-C10 \text{ alkyl})-$, or $-(C2-C10 \text{ alkenyl})-$; and

X is a halogen atom.

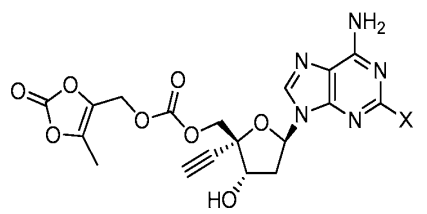
14. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative has a formula (2):



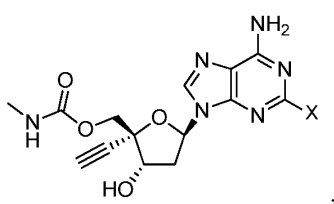
formula (3):



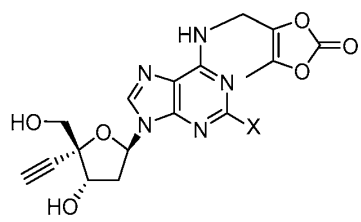
formula (4):



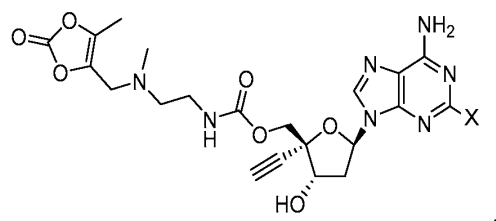
formula (5):



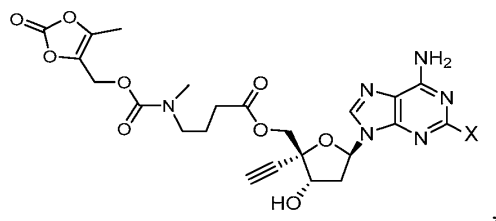
formula (6):



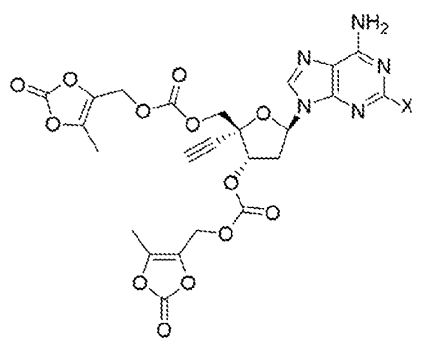
formula (7):



formula (8):

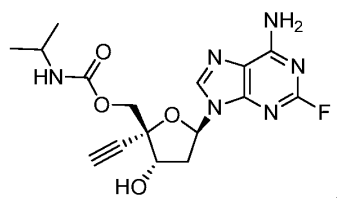


formula (4-B):

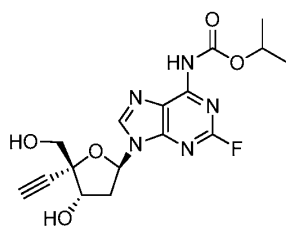


or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof.

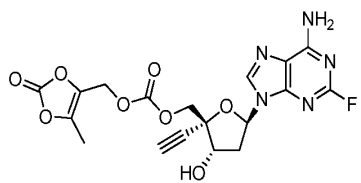
15. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative has a formula (2-A):



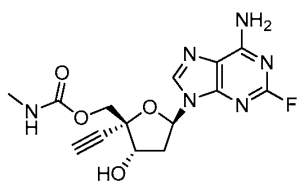
formula (3-A):



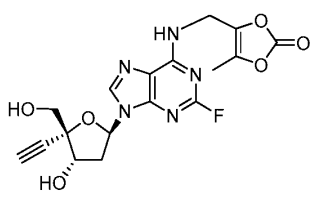
formula (4-A):



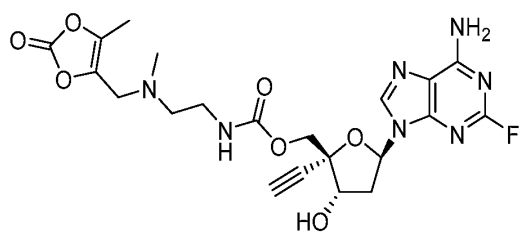
formula (5-A):



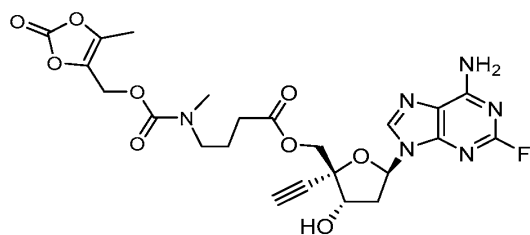
formula (6-A):



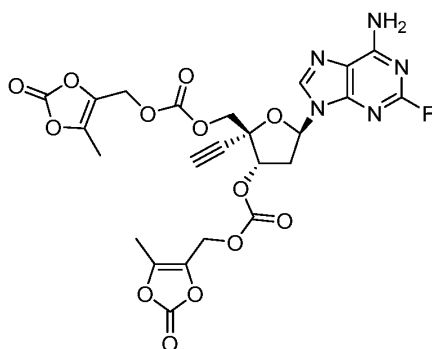
formula (7-A):



formula (8-A):



formula (4-C):

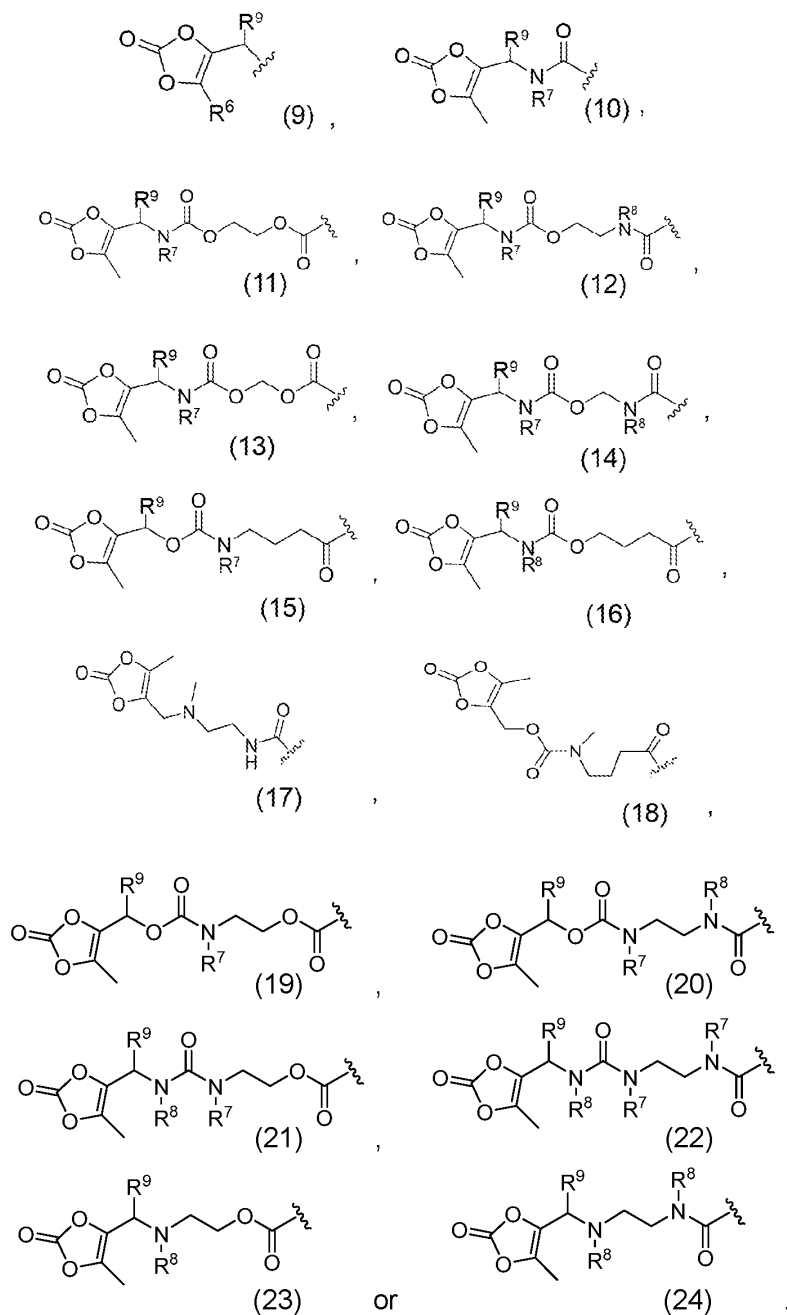


or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof.

16. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative comprises ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate, or a pharmaceutically acceptable salt thereof.
17. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative comprises isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate, or a pharmaceutically acceptable salt thereof.
18. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative comprises ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate, or a pharmaceutically acceptable salt thereof.
19. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative comprises ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-

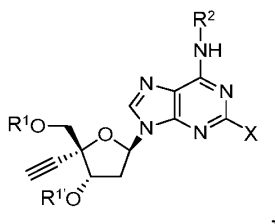
3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate, or a pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative comprises 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one, or a pharmaceutically acceptable salt thereof.
21. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate, or a pharmaceutically acceptable salt thereof.
22. The pharmaceutical composition of embodiment 13, wherein said adenosine derivative is [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate, or a pharmaceutically acceptable salt thereof.
23. The pharmaceutical composition of embodiment 13, wherein said R^5 , $-L^1-R^5$ or $-Z-L^4-R^5$ is selected from formulas 9 – 24:



24. The pharmaceutical composition of any one of embodiments 13-23 further comprising a pharmaceutically acceptable carrier.

25. The pharmaceutical composition of any one of embodiments 13-24 further comprising an effective dosage of one or more HIV antiviral agent selected from abacavir, abacavir sulfate, lamivudine, amprenavir, atazanavir, atazanavir sulfate, AZT, bictagrevir, cabotegravir, darunavir, dideoxycytidine, dideoxyinosine, dolutegravir, doravirine, efavirenz, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, 4'-ethynyl-2'-fluoro-2'-deoxyadenosine, elvitegravir, etravirine, fosamprenavir calcium, indinavir, indinavir sulfate, lamivudine, lopinavir, a combination of lopinavir and ritonavir, darunavir, a combination of darunavir and cobicistat, maraviroc, nelfinavir, nelfinavir mesylate, nevirapine, PPL-100, raltegravir, rilpivirine, stavudine, tipranavir, vicriviroc or a combination thereof.
26. A method for the treatment of a disease, said method comprising administering a subject in need thereof an effective dosage of a pharmaceutical composition comprising an adenosine derivative having a formula (1) or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof:

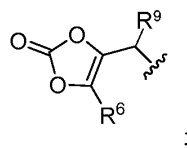


wherein,

R^1 , $R^{1'}$, and R^2 each is independently -H, $-C(O)N(R^3)(R^{3'})$, $-C(O)OR^4$, $-R^5$, $-L^1-R^5$, or $-Z-L^4-R^5$, wherein at least one of R^1 and R^2 is not -H;

R^3 , $R^{3'}$ and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10- membered heterocycloalkyl, aryl, or heteroaryl;

R^5 is:



R^6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, or heteroaryl;

$-L^1-R^5$ is -(C1-C10 alkyl)- $N(R^7)-R^5$, -(C1-C10 alkyl)-O- R^5 , -(C1-C10 alkyl)-S- R^5 , -(C2-C10 alkenyl)- $N(R^7)-R^5$, -(C2-C10 alkenyl)-O- R^5 , -(C2-C10 alkenyl)-S- R^5 , -C(O)O- R^5 , -C(O)O- $L^2-N(R^7)-R^5$, -C(O)O- L^2-O-R^5 , -C(O)O- L^2-S-R^5 , -C(O)O- $L^2-C(O)O-R^5$, -C(O)O- $L^2-C(O)N(R^7)-R^5$, -C(O)O- $L^2-C(O)N(R^7)-L^3-N(R^7)-R^5$, -C(O)O- $L^2-C(O)N(R^7)-L^3-O-R^5$, -C(O)O- $L^2-C(O)N(R^7)-L^3-S-R^5$, -C(O)N(R^7)- R^5 , -C(O)N(R^7)- $L^2-N(R^7)-R^5$, -C(O)N(R^7)- L^2-O-R^5 , -C(O)N(R^7)- L^2-S-R^5 , -C(O)N(R^7)- $L^2-C(O)O-R^5$, -C(O)N(R^7)- $L^2-C(O)N(R^8)-R^5$, -C(O)N(R^7)- $L^2-C(O)N(R^8)-L^3-N(R^7)-R^5$, -C(O)O- $L^2-N(R^7)C(O)O-R^5$, -C(O)N(R^8)- $L^2-N(R^7)C(O)O-R^5$, -C(O)O- $L^2-N(R^7)C(O)N(R^8)-R^5$, -C(O)N(R^7)- $L^2-N(R^7)C(O)N(R^8)-R^5$, -C(O)N(R^7)- $L^2-C(O)N(R^8)-L^3-O-R^5$ or -C(O)N(R^7)- $L^2-C(O)N(R^8)-L^3-S-R^5$;

-Z- is a divalent -C(O)-, -C(O)O-, or -C(O)N(R^7)-;

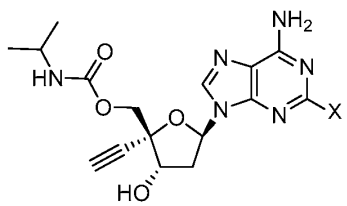
$-L^4-R^5$ is -(C1-C10 alkyl)- $N(R^7)-R^5$, -(C1-C10 alkyl)-O- R^5 , -(C1-C10 alkyl)-S- R^5 , -(C2-C10 alkenyl)- $N(R^7)-R^5$, -(C2-C10 alkenyl)-O- R^5 or -(C2-C10 alkenyl)-S- R^5 ;

R^7 , R^8 and R^9 each is independently -H, C1-C10 alkyl, or C2-C10 alkenyl;

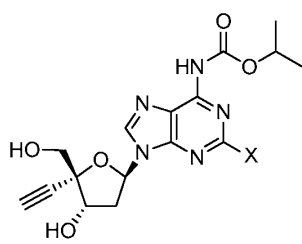
L^2 and L^3 each is intendedly divalent -(C1-C10 alkyl)-, or -(C2-C10 alkenyl)-; and

X is a halogen atom.

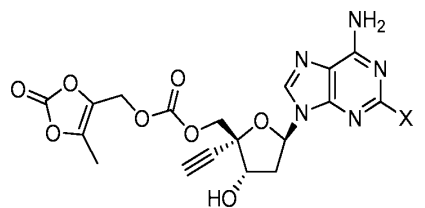
27. The method of embodiment 26, wherein said adenosine derivative has a formula (2):



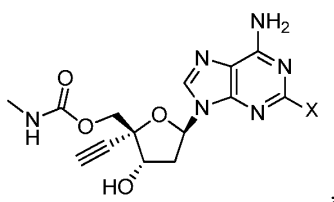
formula (3):



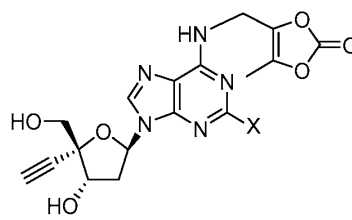
formula (4):



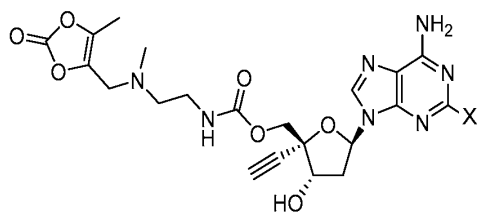
formula (5):



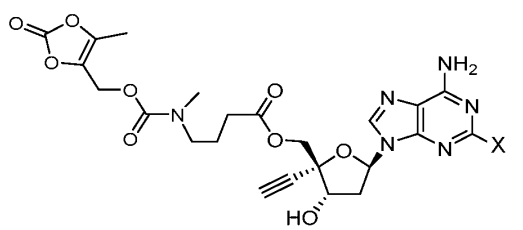
formula (6):



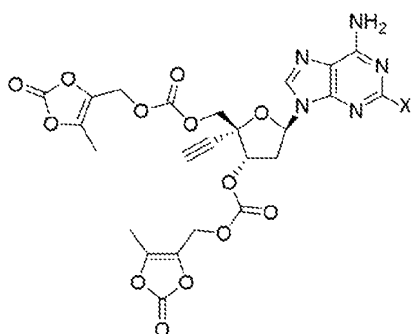
formula (7):



formula (8):

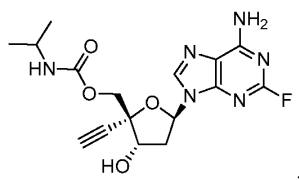


formula (4-B):

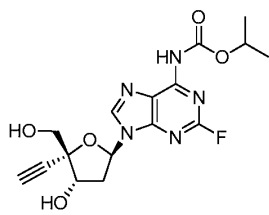


or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof.

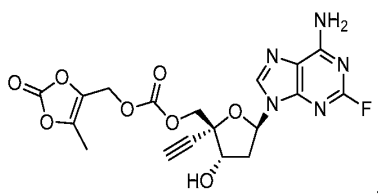
28. The method of embodiment 26, wherein said adenosine derivative has a formula (2-A):



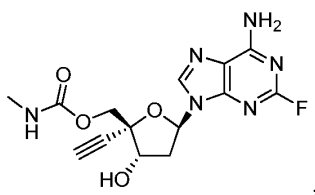
formula (3-A):



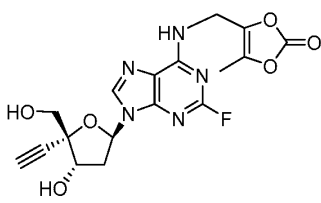
formula (4-A):



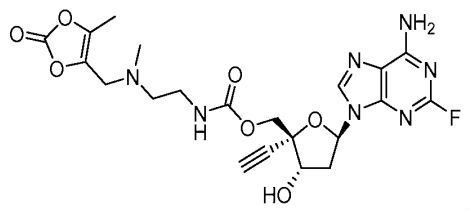
formula (5-A):



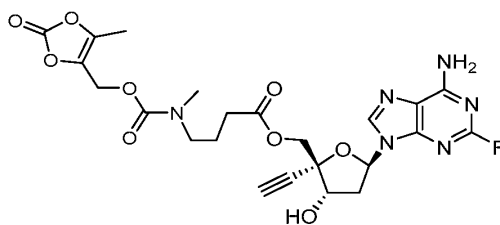
formula (6-A):



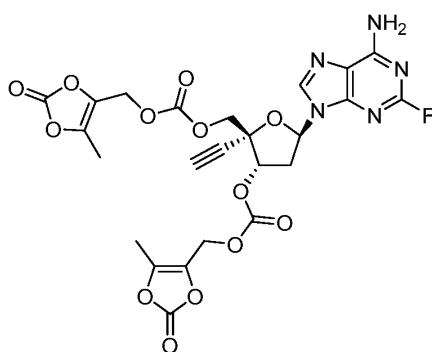
formula (7-A):



formula (8-A):



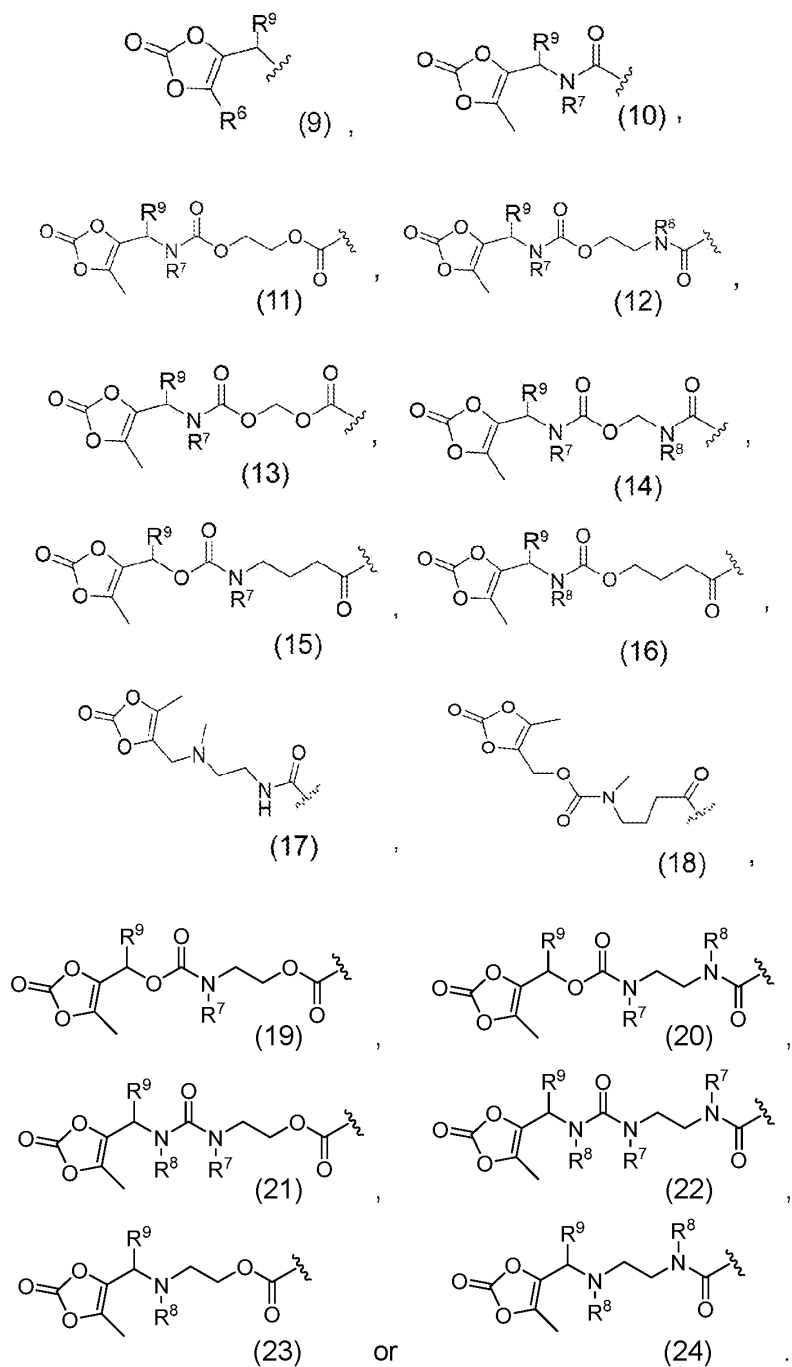
formula (4-C):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof.

29. The method of embodiment 26, wherein said adenosine derivative comprises ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate, or a pharmaceutically acceptable salt thereof.
30. The method of embodiment 26, wherein said adenosine derivative comprises isopropyl (9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)carbamate, or a pharmaceutically acceptable salt thereof.
31. The method of embodiment 26, wherein said adenosine derivative comprises ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate, or a pharmaceutically acceptable salt thereof.

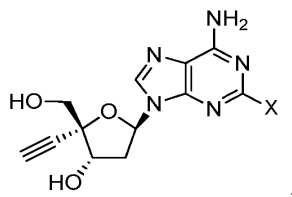
32. The method of embodiment 26, wherein said adenosine derivative comprises ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl methylcarbamate, or a pharmaceutically acceptable salt thereof.
33. The method of embodiment 26, wherein said adenosine derivative comprises 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one, or a pharmaceutically acceptable salt thereof.
34. The method of embodiment 26, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate, or a pharmaceutically acceptable salt thereof.
35. The method of embodiment 26, wherein said adenosine derivative is [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate, or a pharmaceutically acceptable salt thereof.
36. The method of embodiment 26, wherein said adenosine derivative comprises said R^5 , $-L^1-R^5$ or $-Z-L^4-R^5$ selected from formulas 9 – 24:



37. The method of any one of embodiments 26-36, said pharmaceutical composition is administered to said subject via intramuscular (IM) injection, subcutaneous

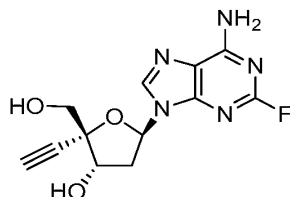
(SC) injection, intravenous (IV) injection, oral administration, topical application, implant application or a combination thereof.

38. The method of any one of embodiments 26-37 further comprising measuring a specimen of said subject to determine a measured level of a target drug in said specimen, wherein said target drug has a formula (T-1):



an isomer thereof, or a pharmaceutically acceptable salt thereof.

39. The method of embodiment 38, wherein said target drug has a formula (T-1A):



an isomer thereof, or a pharmaceutically acceptable salt thereof.

40. The method of embodiment 38, wherein said target drug is (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol, or a pharmaceutically acceptable salt thereof.
41. The method of any one of embodiments 38-40 further comprising adjusting said effective dosage to produce a modified effective dosage if said measured level of said target drug is different from a predetermined target level of said target drug and administering said modified effective dosage to said subject.

42. The method of any one of embodiments 26-41, wherein said disease is Acquired Immune Deficiency Syndrome (AIDS), wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV.
43. The method of any one of embodiments 26-42 further comprising administering said subject an effective dosage of one or more anti-HIV agents selected from abacavir, abacavir sulfate, lamivudine, amprenavir, atazanavir, atazanavir sulfate, AZT, bictagrevir, cabotegravir, darunavir, dideoxycytidine, dideoxyinosine, dolutegravir, doravirine, efavirenz, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, 4'-ethynyl-2'-fluoro-2'-deoxyadenosine, elvitegravir, etravirine, fosamprenavir calcium, indinavir, indinavir sulfate, lamivudine, lopinavir, a combination of lopinavir and ritonavir, darunavir, a combination of darunavir and cobicistat, maraviroc, nelfinavir, nelfinavir mesylate, nevirapine, PPL-100, raltegravir, rilpivirine, stavudine, tipranavir, vicriviroc or a combination thereof.
44. The method of embodiment 43, wherein said adenosine derivative and said one or more anti-HIV agents are administered to said subject together or separately via oral administration, parenteral administration or a combination thereof.
45. The method of embodiment 44, wherein said adenosine derivative and said one or more anti-HIV agents are administered to said subject with a daily, weekly, biweekly or monthly administration schedule.
46. A use of the pharmaceutical composition of any one of embodiments 13-25 for the treatment of a disease in a subject in need thereof, wherein said disease is Acquired Immune Deficiency Syndrome (AIDS), wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV.
47. A use of the method of any one of embodiments 26-45 for the treatment of a disease in a subject in need thereof, wherein said disease is Acquired Immune Deficiency Syndrome (AIDS), wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV.

48. Use of the adenosine derivative of any one of embodiments 1-12 for manufacturing a medicament for treating a disease, wherein said disease is Acquired Immune Deficiency Syndrome (AIDS), wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV.
49. A method for the prevention of infection in a subject in need thereof, said method comprising administering said subject an effective dosage of a pharmaceutical composition of any one of embodiments 13-25, wherein said subject is free from detectable symptoms of said infection.
50. The method of embodiment 49, wherein said infection comprises a disease selected from Acquired Immune Deficiency Syndrome (AIDS), an infection of wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV, or a combination thereof.
51. The method of embodiment 50, wherein said detectable symptoms comprise symptoms of Acquired Immune Deficiency Syndrome (AIDS), symptoms of infection of HIV viruses comprising wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, multidrug resistant HIV, or a combination thereof.
52. The method of embodiment 51, wherein said pharmaceutical composition administered to said subject with a daily, weekly, biweekly or monthly administration schedule.
53. The method of embodiment 52 further comprising administering said subject an effective dosage of one or more anti-HIV agents selected from abacavir, abacavir sulfate, lamivudine, amprenavir, atazanavir, atazanavir sulfate, AZT, bictagrevir, cabotegravir, darunavir, dideoxycytidine, dideoxyinosine, dolutegravir, doravirine, efavirenz, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, 4'-ethynyl-2-fluoro-2'-deoxyadenosine, elvitegravir, etravirine, fosamprenavir calcium, indinavir, indinavir sulfate, lamivudine, lopinavir, a combination of lopinavir and ritonavir, darunavir, a combination of darunavir and cobicistat, maraviroc, nelfinavir, nelfinavir mesylate, nevirapine, PPL-100, raltegravir, rilpivirine, stavudine, tipranavir, vicriviroc or a combination thereof.

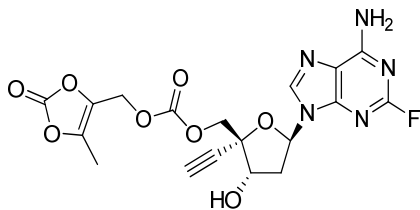
54. The method of embodiment 53, wherein said one or more anti-HIV agents are administered to said subject together with said pharmaceutical composition or separately.
55. A method for treating HIV infection, comprising: administering a subject in need thereof an effective dosage of the pharmaceutical composition of any one of embodiment 1-25.
56. A method for preventing HIV infection, comprising: administering a subject in need thereof an effective dosage of the pharmaceutical composition of any one of embodiment 1-25.
57. The method of embodiment 55 or 56, wherein the HIV infection is caused by wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV.
58. The method of any one of embodiment 55-57, wherein the administration is by oral administration.
59. The method of any one of embodiment 55-57, wherein the administration is by parenteral administration.
60. The method of embodiment 59, wherein the parenteral administration is by intramuscular or subcutaneous injection.
61. The method of any one of embodiments 55-60, wherein the administration of the pharmaceutical composition results in a higher plasma concentration of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
62. The method of embodiment 61, wherein the administration of the pharmaceutical composition results in at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or 200% higher plasma concentration of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
63. The method of embodiment 61, wherein the administration of the pharmaceutical composition results in 50%-80%, 50%-100%, or 50%-200% higher plasma

concentration of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.

64. The method of any one of embodiments 55-63, wherein the administration of the pharmaceutical composition results in a prolonged release of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
65. The method of any one of embodiments 55-64, wherein the administration of the pharmaceutical composition results in a higher AUC of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
66. The method of embodiment 65, wherein the administration of the pharmaceutical composition results in at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% higher AUC of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
67. The method of embodiment 65, wherein the administration of the pharmaceutical composition results in 50%-200%, 50%-150%, or 80%-120% higher AUC of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
68. The method of any one of embodiments 55-67, wherein the administration of the pharmaceutical composition results in a higher $C_{\max}$ of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
69. The method of embodiment 68, wherein the administration of the pharmaceutical composition results in at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% higher $C_{\max}$ of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
70. The method of embodiment 68, wherein the administration of the pharmaceutical composition results in 50%-200%, 50%-150%, or 80%-100% higher $C_{\max}$ of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.

CLAIMS

1. An adenosine derivative of formula (4-A):



(formula (4-A),

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising an adenosine derivative of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
3. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition is suitable for oral administration.
4. The pharmaceutical composition of claim 2 or 3, wherein the pharmaceutical composition is a liquid dosage form.
5. The pharmaceutical composition of claim 4, wherein the liquid dosage form is a solution, an emulsion or a liquid suspension.
6. The pharmaceutical composition of claim 2 or 3, wherein the pharmaceutical composition is a solid dosage form.
7. The pharmaceutical composition of claim 6, wherein the solid dosage form is a tablet, capsule, granule, powder, sachet, reconstitutable powder, inhalable dry powder, or chewable.
8. Use of an adenosine derivative of claim 1 or a pharmaceutical composition of any one of claims 2-7 in the manufacture of a medicament for treating HIV infection in a subject.

9. Use of an adenosine derivative of claim 1 or a pharmaceutical composition of any one of claims 2-7 in the manufacture of a medicament for preventing HIV infection in a subject.
10. The use of claim 8 or 9, wherein the HIV infection is caused by wild-type HIV-1, NRTI-resistant HIV-1, HIV-2, HIV having M184V mutations, HIV having K65R, or multidrug resistant HIV.
11. The use of any one of claims 8-10, wherein the adenosine derivative or pharmaceutical composition is to be administered orally to the subject.
12. The use of claim 11, wherein the administration of the adenosine derivative or the pharmaceutical composition to the subject results in a higher plasma concentration of 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) when compared to administration of a dose-equivalent EFdA under the same condition.
13. The use of claim 12, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in at least a 10% higher plasma concentration of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
14. The use of any one of claims 11-13, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in a higher AUC of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
15. The use of claim 14, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in at least 10% higher AUC of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
16. The use of any one of claims 11-15, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in a higher $C_{\max}$ of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.
17. The use of claim 16, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in at least a 10% higher $C_{\max}$ of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.

18. The adenosine derivative of claim 1 or a pharmaceutical composition of any one of claims 2-7 for use as a medicament.