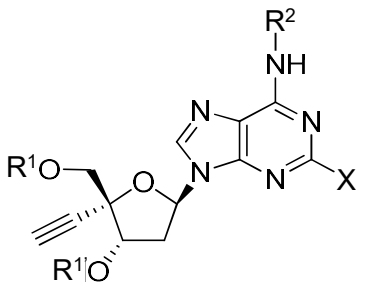
CLAIMS

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



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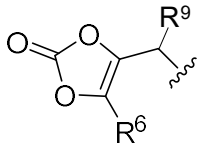
wherein,

R^1 and, $R^{1'}$, ~~and R^2~~ each is independently ~~-H~~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~~H;

R^2 is H, -C(O)OR^4, or -R^5;

R^3, $R^{3'}$ and R^4 each is independently ~~-H~~H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3-10 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 alkylene)-N(R^7)-R^5, -(C1-C10 alkylene)-O-R^5, -(C1-C10 alkylene)-S-R^5, -(C2-C10 alkenylene)-N(R^7)-R^5, -(C2-C10 alkenylene)-O-R^5, -(C2-C10 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)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, -$C(O)N(R^7)$-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, -$C(O)N(R^7)$-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 alkylene)-$N(R^7)$-R^5, -(C1-C10 alkylene)-O-R^5, -(C1-C10 alkyl)-S-R^5, -(C2-C10 alkenylene)-$N(R^7)$-R^5, -(C2-C10 alkenylene)-O-R^5, ~~or~~ -(C2-C10 alkenylene)-S-R^5 or -(C3 alkylene)-$N(R^7)$-C(O)-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.

2. The adenosine derivative of claim 1, wherein R^1 ~~and R^2 each~~ is independently ~~-H~~H, -$C(O)N(R^3)(R^{3'})$, ~~-R^5,~~ -L^1-R^5, or -Z-L^4-R^5.

3. The adenosine derivative of claim 1 or 2, wherein ~~R^1 and~~ R^2 each is independently ~~-H~~H~~,~~ or -R^5~~, or -L1-R5~~.

4. The adenosine derivative of any one of claims 1-3, wherein R^1 is -L^1-R^5.

5. The adenosine derivative of any one of claims 1-4, wherein $R^{1'}$ is H or -L^1-R^5.

6. The adenosine derivative of any one of claims 1-4, wherein $R^{1'}$ is H.

7. The adenosine derivative of any one of claims 1-6, wherein-L^1-R^5 is selected from the group consisting of C(O)O-R^5 ~~-(C1-C10 alkylene)-$N(R^7)$-R^5, -(C1-C10 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-.

8. The adenosine derivative of any one of claims 1-7, wherein -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, or~~ 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-~~.

9. The adenosine derivative of any one of claims 1-7, wherein -L^1-R^5 is -$C(O)O$-R^5.

10. The adenosine derivative of any one of claims 1-9, wherein R^2 is H.

11. The adenosine derivative of claim 1, wherein R^3 and $R^{3'}$ each is independently H, C1-C10 alkyl, or C3-C6 cycloalkyl.

12. The adenosine derivative of claim 1, wherein R^3 and $R^{3'}$ each is independently H or C1-C3 alkyl.

13. The adenosine derivative of claim 1, wherein R^4 is C1-C10 alkyl, or C3-C6 cycloalkyl.

14. The adenosine derivative of claim 1 or 2, wherein -Z-L^4-R^5 is Z-(C1-C10 alkylene)-N(R^7)-R^5, Z-(C3 alkylene)-N(R^7)-C(O)-R^5, or Z-(C1-C10 alkylene)-O-R^5.

15. The adenosine derivative of any one of claims 1, 2, and 14, wherein -Z- is -C(O)- or -C(O)N(R^7)-.

16. The adenosine derivative of any one of claims 1-15, wherein R^6 is C1-C5 alkyl.

17. The adenosine derivative of claim 16, wherein R^6 is methyl.

18. The adenosine derivative of any one of claims 1-17, wherein R^7 and R^8 is each independently H or C1-C5 alkyl.

19. The adenosine derivative of claim 18, wherein R^7 and R^8 is each independently H or methyl.

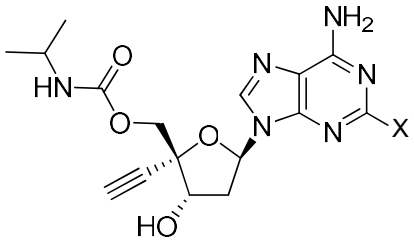
~~20. The adenosine derivative of any one of claims 1-19, wherein R^8 is each independently H or C1-C5 alkyl.~~

~~21. The adenosine derivative of claim 20, wherein R^8 is each independently H or methyl.~~

~~22.~~20. The adenosine derivative of any one of claims 1-~~21~~19, wherein R^9 is H or Me.

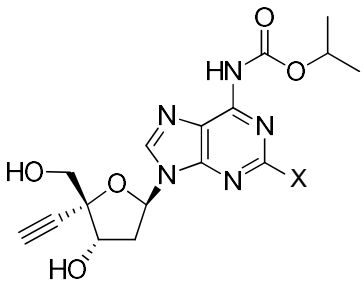
~~23. The adenosine derivative of claim 22, wherein R^9 is H.~~

~~24.~~21. The adenosine derivative of claim 1, wherein said adenosine derivative has a formula (2):



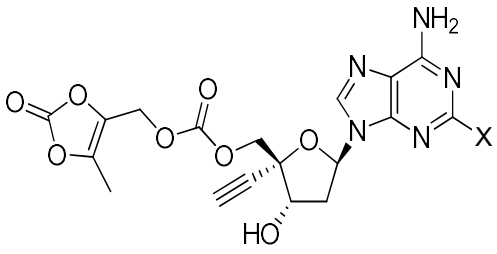
,

formula (3):



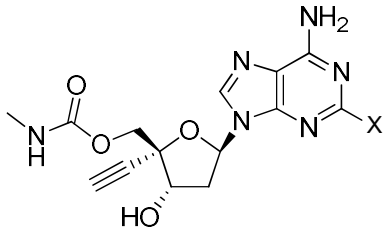
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formula (4):



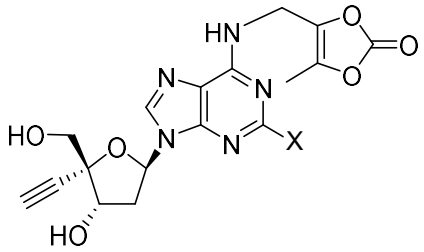
,

formula (5):



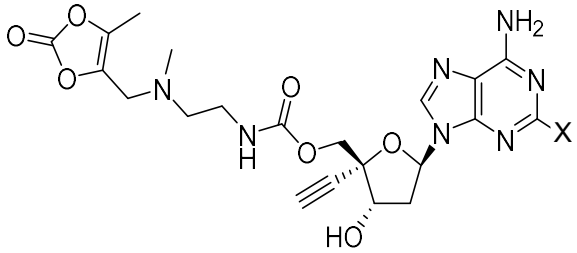
,

formula (6):



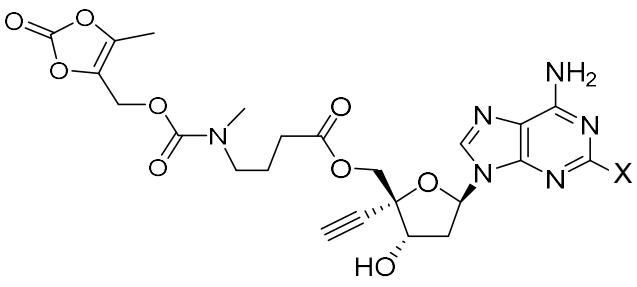
,

formula (7):



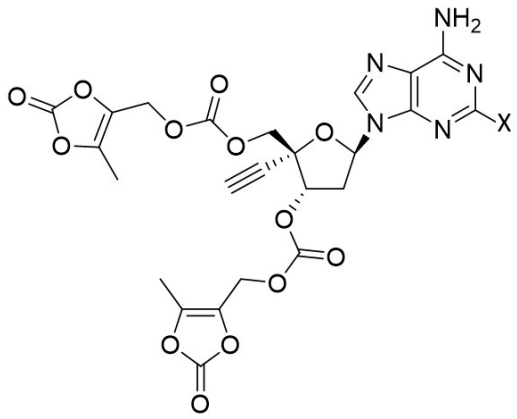
,

formula (8):



,

formula (4-B):

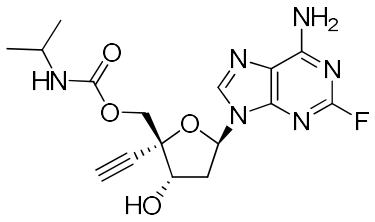


,

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

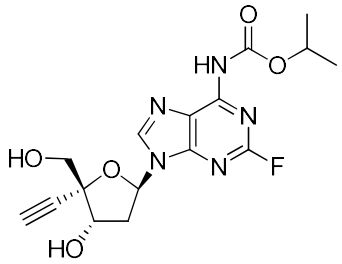
~~25.~~22. The adenosine derivative of claim 1, wherein said adenosine derivative is a compound that has a structure of:

formula (2-A):



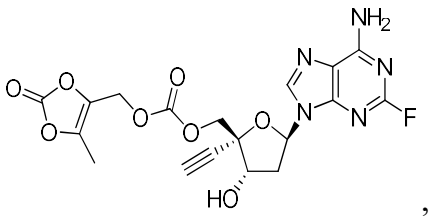
,

formula (3-A):

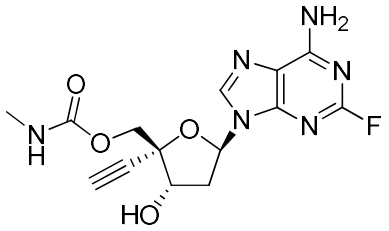


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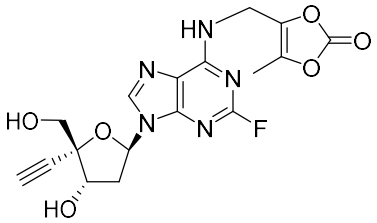
formula (4-A):


,

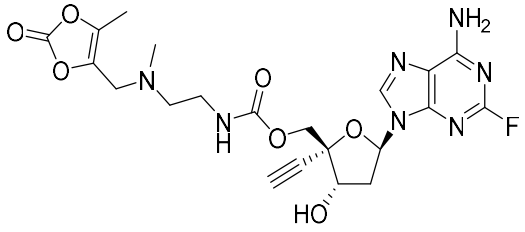
formula (5-A):


,

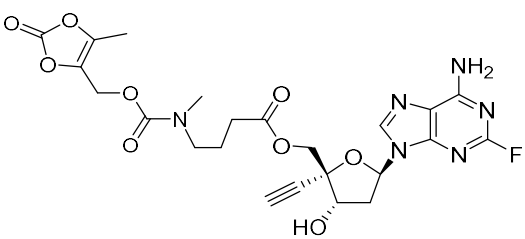
formula (6-A):


,

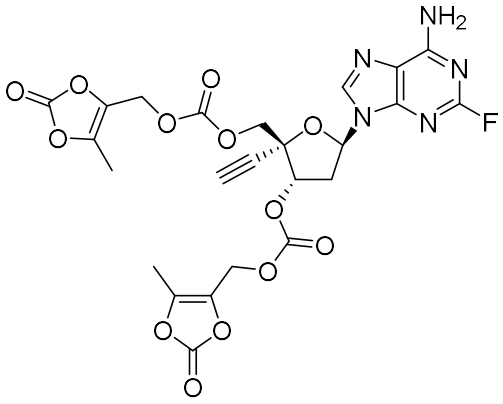
formula (7-A):


,

formula (8-A):


,

formula (4-C):

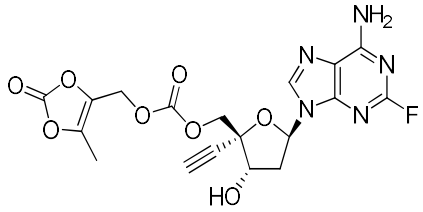


,

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

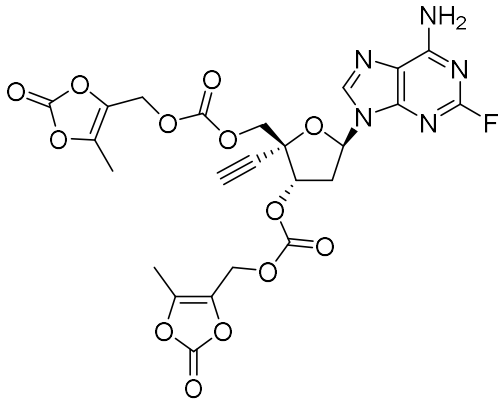
~~26.~~23. The adenosine derivative of claim 1, wherein said adenosine derivative is ~~((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropylcarbamate~~a compound having the structure of:

formula (4-A):



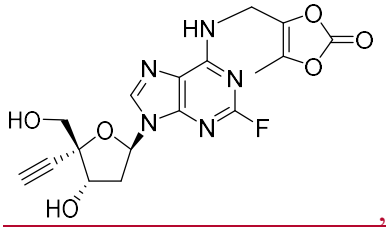
,

formula (4-C):



, or

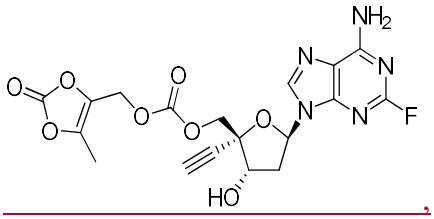
formula (6-A):



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

~~27.~~24. The adenosine derivative of claim 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~~a compound having the structure of:

formula (4-A)



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

~~28. The adenosine derivative of claim 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.~~

~~29. The adenosine derivative of claim 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.~~

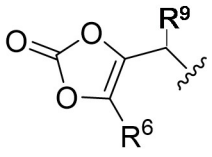
~~30. The adenosine derivative of claim 1, wherein said adenosine derivative is 4-(((9-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-fluoro-9H-purin-6-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one.~~

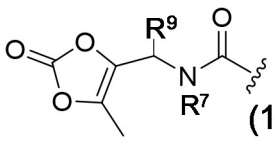
~~31. The adenosine derivative of claim 1, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl (2-(methyl((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)ethyl)carbamate.~~

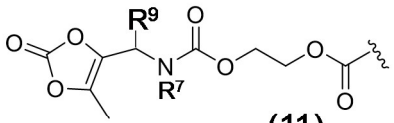
~~32. The adenosine derivative of claim 1, wherein said adenosine derivative is [(2R,3S,5R)-5-(6-amino-2-fluoro-purin-9-yl)-2-ethynyl-3-hydroxy-tetrahydrofuran-2-yl]methyl 4-[methyl-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]amino]butanoate.~~

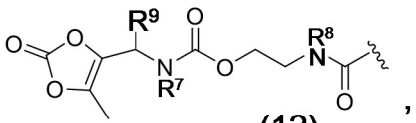
~~33. The adenosine derivative of claim 1, wherein said adenosine derivative is ((2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-3-((((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)oxy)tetrahydrofuran-2-yl)methyl ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) carbonate.~~

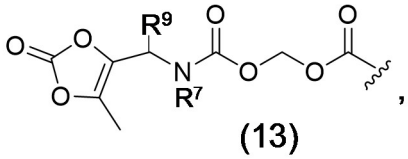
~~34.~~25. The adenosine derivative of claim 1, wherein said R^5, $-L^1-R^5$ or $-Z-L^4-R^5$ is selected from formulas 9 – 24:

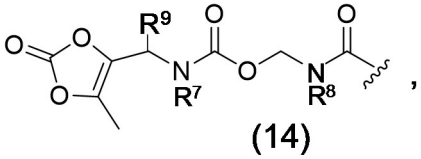

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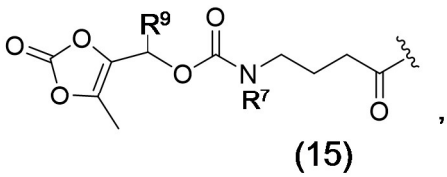

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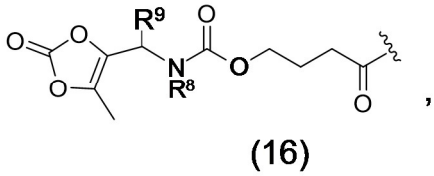

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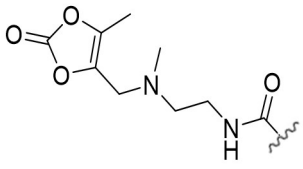

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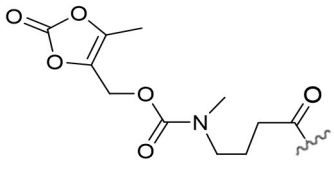

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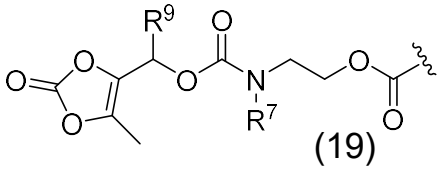

(14) ,


(15) ,

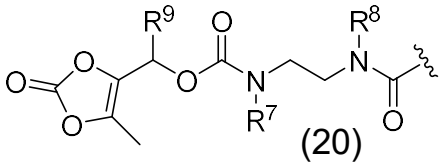

(16) ,


(17) ,

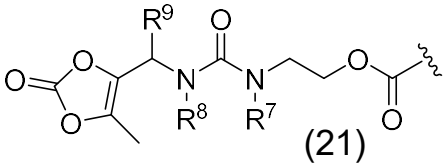

(18) ,



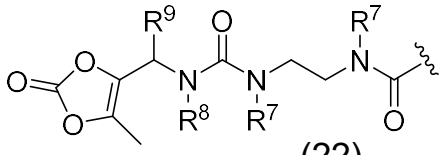
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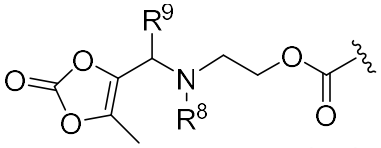
(20) ,



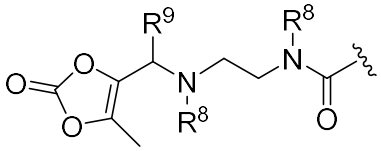
(21) ,



(22) ,



(23) or



(24) .

~~35.~~26. The adenosine derivative of any one of claims 1-~~34~~25, wherein said adenosine derivative comprises a reverse transcriptase inhibitor activity in vivo, a reverse transcriptase chain terminator activity in vivo, a DNA translocation inhibitor activity in vivo, or a combination thereof.

~~36.~~27. A pharmaceutical composition comprising an adenosine derivative of any one of claims 1-~~35~~ 26 and a pharmaceutically acceptable carrier.

~~37.~~28. The pharmaceutical composition of claim ~~36~~27, wherein the pharmaceutical composition is suitable for oral administration.

~~38.~~29. The pharmaceutical composition of claim ~~36~~27, wherein the pharmaceutical composition is suitable for parenteral administration.

~~39.~~30. The pharmaceutical composition of claim ~~38~~29, wherein the pharmaceutical composition is a long-acting injectable composition.

~~40.~~31. The pharmaceutical composition of claim ~~38~~ 29 or ~~39~~30, wherein the pharmaceutical composition is suitable for intramuscular or subcutaneous injection.

~~41.~~32. The pharmaceutical composition of any one of claims ~~36-40~~27-31, wherein the pharmaceutical composition is a liquid dosage form.

42.33. The pharmaceutical composition of claim 4132, wherein the liquid dosage form is a solution, an emulsion or a liquid suspension.

43.34. The pharmaceutical composition of any one of claims 36-4027-31, wherein the pharmaceutical composition is a solid dosage form.

44.35. The pharmaceutical composition of claim 4334, wherein the solid dosage form is a tablet, capsule, granule, powder, sachet, reconstitutable powder, inhalable dry powder, or chewable.

45.36. The pharmaceutical composition of any one of claims 36-4427-35, wherein the pharmaceutically acceptable carrier comprises acacia, animal oil, benzyl alcohol, benzyl benzoate, calcium stearate, carbomer, 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, hydroxpropyl 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 glycol, 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 oil, water, xanthan gum, or any combination thereof.

46.37. The pharmaceutical composition of claim 4536, wherein the pharmaceutically acceptable carrier comprises polyethylene glycol 400.

~~47.~~38. ~~A method for treating HIV infection, comprising: administering a subject in need thereof an effective dosage of the~~ Use of an adenosine derivative of any one of claims 1-26 or a pharmaceutical composition of any one of claims ~~36-46~~27-37 in the manufacture of a medicament for treating HIV infection in a subject.

~~48.~~39. ~~A method for preventing HIV infection, comprising: administering a subject in need thereof an effective dosage of the~~ Use of an adenosine derivative of any one of claims 1-26 or a pharmaceutical composition of any one of claims ~~36-46~~27-37 in the manufacture of a medicament for preventing HIV infection in a subject.

~~49.~~40. The ~~method~~ use of claim ~~47~~ 38 or ~~48~~39, 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.

~~50.~~41. The ~~method~~ use of any one of claims ~~47-49~~38-40, wherein the ~~administration~~ adenosine derivative or pharmaceutical composition is to be ~~by oral administration~~administered orally to the subject.

~~51.~~42. The ~~method~~ use of any one of claims ~~47-49~~38-40, wherein the adenosine derivative or pharmaceutical composition~~administration~~ is to be administered ~~by parenteral administration~~parentally to the subject.

~~52.~~43. The ~~method~~ use of claim ~~51~~42, wherein the parenteral administration is by intramuscular or subcutaneous injection.

~~53.~~44. The ~~method~~ use of any one of claims ~~47-52~~41-43, wherein the administration of the adenosine derivative or the pharmaceutical composition to the subject results in a higher plasma concentration of 4'-ethynyl-2fluoro-2'-deoxyadenosine (EFdA) when compared to administration of a dose-equivalent EFdA under the same condition.

~~54.~~45. The ~~method~~ use of claim ~~53~~44, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in at least a 10%, 20%, 30%, 40%, or 50% higher plasma concentration of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.

~~55.~~46. The ~~method~~ use of any one of claims ~~47-54~~41-45, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in a prolonged release of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.

~~56.~~47. The ~~method~~ use of any one of claims ~~47-55~~41-46, 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.

~~57.~~48. The ~~The method~~use of claim ~~56~~47, 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.

~~58.~~49. The ~~method~~ use of any one of claims ~~47-57~~41-48, 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.

~~59.~~50. The ~~method~~ use of claim ~~58~~49, wherein the administration of the adenosine derivative or pharmaceutical composition to the subject results in at least a 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.

51. The adenosine derivative of any one of claims 1-26 or a pharmaceutical composition of any one of claims 27-37 for use as a medicament.