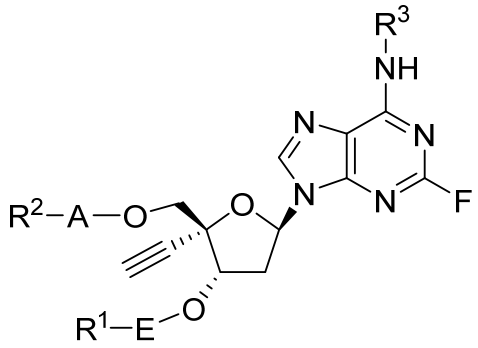
CLAIMS

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



(I)

wherein:

A and E are each independently selected from the group consisting of a bond, -(CO)-, -(CO)-G-, -(CO)-G-(C_{1-10}alkylene)-J-, -(CO)-G-(C_{2-10}alkenylene)-J-, and -(CO)-G-(C_{2-10}alkynylene)-J-;

G is selected form the group consisting of a bond, O, NH, and S;

J is selected form the group consisting of a bond, O, NH, S, and -(CO)-G-;

R^1 is selected from the group consisting of H, C_{1-20}alkyl, C_{1-20}haloalkyl, C_{1-20}alkoxy, C_{2-20}alkenyl, C_{2-20}alkynyl, C_{3-20}cycloalkyl, 3- to 20-membered heterocycloalkyl, aryl, and heteroaryl;

R^2 is selected from the group consisting of H, C_{1-20}alkyl, C_{1-20}haloalkyl, C_{1-20}alkoxy, C_{2-20}alkenyl, C_{2-20}alkynyl, C_{3-20}cycloalkyl, 3- to 20-membered heterocycloalkyl, aryl, and heteroaryl, wherein at least one of R^1 and R^2 is adamantyl;

or R^1 and R^2 taken together with the atoms to which they are attached form a 3- to 25-membered heterocyclic ring; and

R^3 is selected from the group consisting of H, -(CO)-G-C_{1-10}alkyl, C_{1-10}alkyl, C_{1-10}haloalkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-12}cycloalkyl, 3- to 12-membered heterocycloalkyl, aryl, and heteroaryl.

2. The adenosine derivative of claim 1, wherein A is selected from the group consisting of a bond, -(CO)-, -(CO)-G-, and -(CO)-G-(C_{1-5}alkylene)-J-.

3. The adenosine derivative of claim 1 or 2, wherein A is -(CO)-G- or -(CO)-G-(C_{1-5}alkylene)-J-.

4. The adenosine derivative of any one of claims 1-3, wherein E is a bond, -(CO)-G-, and -(CO)-G-(C_{1-5}alkylene)-J-.

5. The adenosine derivative of any one of claims 1-4, wherein E is a bond.

6. The adenosine derivative of any one of claims 1-5, wherein G is a bond or O.

7. The adenosine derivative of any one of claims 1-6, wherein J is a bond or O.

8. The adenosine derivative of any one of claims 1-7, wherein G is O and J is a bond.

9. The adenosine derivative of any one of claims 1-8, wherein R^1 is H, C_{1-5}alkyl, or adamantyl.

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

11. The adenosine derivative of any one of claims 1-10, wherein R^2 is H, C_{1-5}alkyl, or adamantyl.

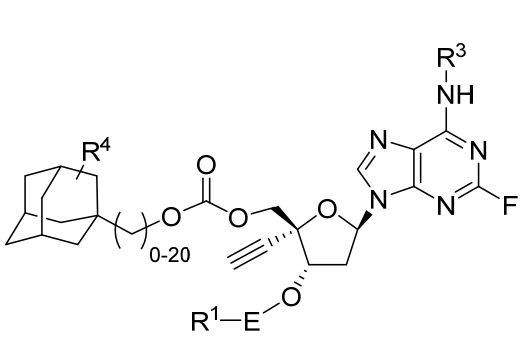
12. The adenosine derivative of any one of claims 1-11, wherein R^2 is adamantyl.

13. The adenosine derivative of any one of claims 1-8, wherein R^1 and R^2 taken together with the atoms to which they are attached form a 6- to 15-membered heterocyclic ring.

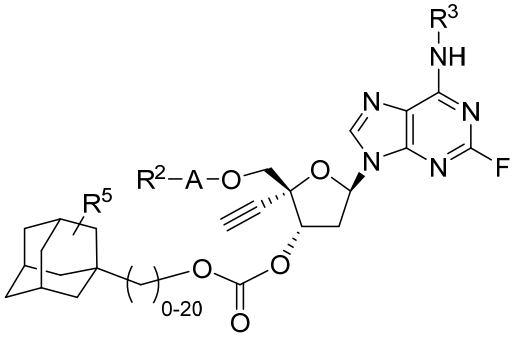
14. The adenosine derivative of any one of claims 1-13, wherein R^3 is -(CO)-C_{1-5}alkyl, -(CO)-O-C_{1-5}alkyl, or C_{1-5}alkyl.

15. The adenosine derivative of any one of claims 1-14, wherein R^3 is H.

16. The adenosine derivative, pharmaceutically acceptable salt, tautomer, or solvate of claim 1, which is a compound of formula (Ie), (If), or a pharmaceutically acceptable salt, tautomer, or solvate thereof:



(Ie),



(If)

wherein:

A and E are each independently selected from the group consisting of a bond, -(CO)-, -(CO)-G-, -(CO)-G-(C_{1-10}alkylene)-J-, -(CO)-G-(C_{2-10}alkenylene)-J-, and -(CO)-G-(C_{2-10}alkynylene)-J-;

G is selected form the group consisting of a bond, O, NH, and S;

J is selected form the group consisting of a bond, O, NH, S, and -(CO)-G-;

R^1 is selected from the group consisting of H, C_{1-10}alkyl, C_{1-10}haloalkyl, C_{1-10}alkoxy, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-20}cycloalkyl, 3- to 20-membered heterocycloalkyl, aryl, and heteroaryl;

R^2 is selected from the group consisting of H, C_{1-10}alkyl, C_{1-10}haloalkyl, C_{1-10}alkoxy, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-20}cycloalkyl, 3- to 20-membered heterocycloalkyl, aryl, and heteroaryl;

R^3 is selected from the group consisting of H, -(CO)-O-C_{1-10}alkyl, and C_{1-10}alkyl;

R^4 is selected from the group consisting of H, C_{1-10}alkyl, C_{1-10}haloalkyl, C_{1-10}alkoxy, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-12}cycloalkyl, 3- to 12-membered heterocycloalkyl, aryl, and heteroaryl; and

R^5 is selected from the group consisting of H, C_{1-10}alkyl, C_{1-10}haloalkyl, C_{1-10}alkoxy, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-12}cycloalkyl, 3- to 12-membered heterocycloalkyl, aryl, and heteroaryl.

17. The adenosine derivative of claim 16, wherein A and E are each independently selected from the group consisting of a bond, -(CO)-, -(CO)-G-, and -(CO)-G-(C_{1-5}alkylene)-J-.

18. The adenosine derivative of claim 17, wherein A is -(CO)-G- or -(CO)-G-(C_{1-5}alkylene)-J-.

19. The adenosine derivative of any one of claims 16-18, wherein E is a bond.

20. The adenosine derivative of any one of claims 16-19, wherein G is a bond or O.

21. The adenosine derivative of any one of claims 16-20, wherein J is a bond or O.

22. The adenosine derivative of any one of claims 16-21, wherein G is O and J is a bond.

23. The adenosine derivative of any one of claims 16-22, wherein R^1 is H, C_{1-5}alkyl, or adamantyl.

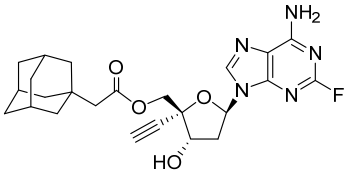
24. The adenosine derivative of any one of claims 16-23, wherein R^1 is H.

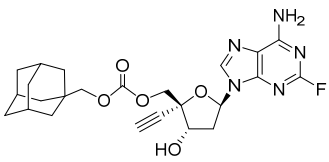
25. The adenosine derivative of any one of claims 16-22, wherein R^2 is H, C_{1-5}alkyl, or adamantyl.

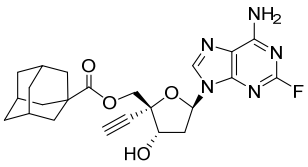
26. The adenosine derivative of any one of claims 16-22 and 25, wherein R^2 is adamantyl.

27. The adenosine derivative of any one of claims 16-26, wherein R^3 is H.

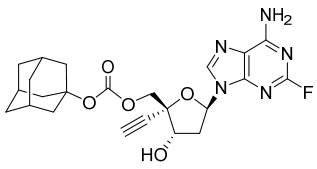
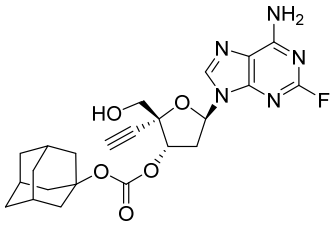
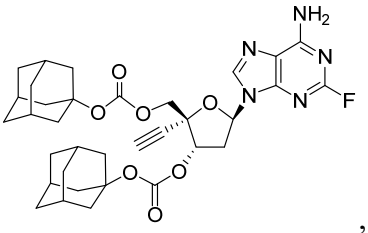
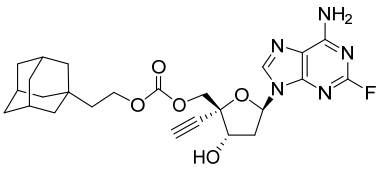
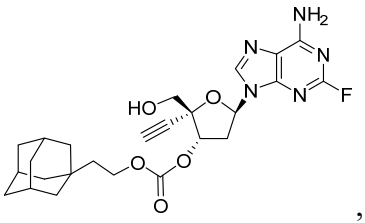
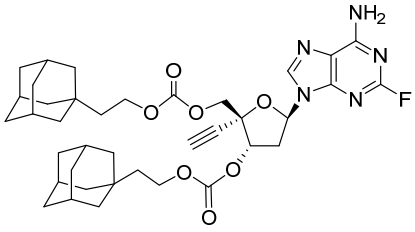
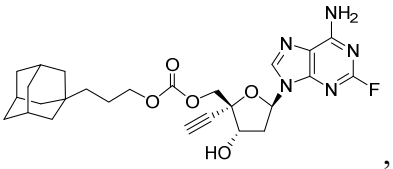
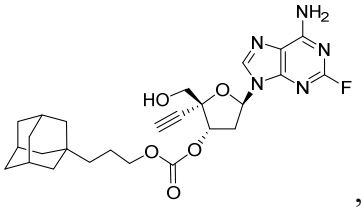
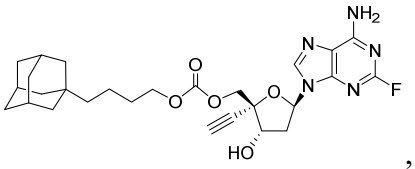
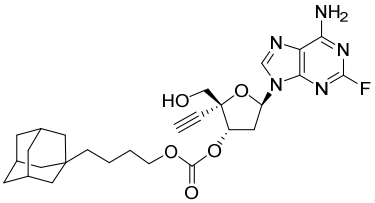
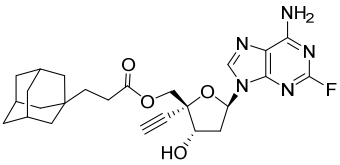
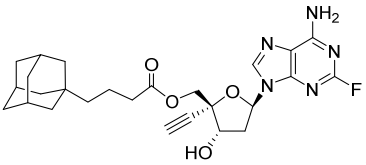
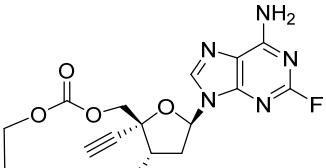
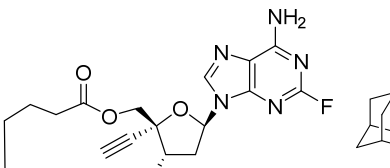
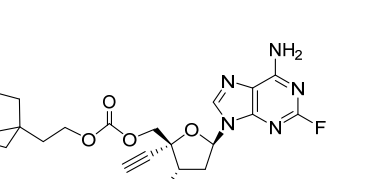
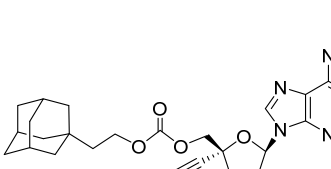
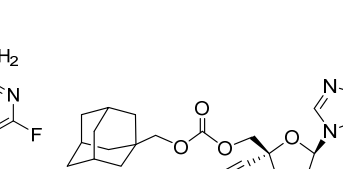
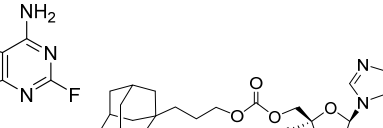
28. The adenosine derivative, pharmaceutically acceptable salt, tautomer, or solvate of claim 1, which is selected from the group consisting of:

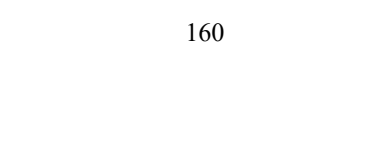


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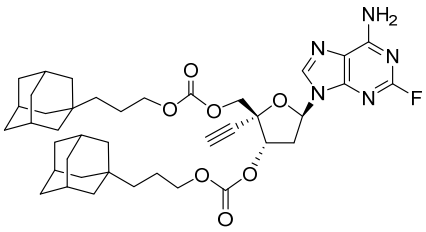
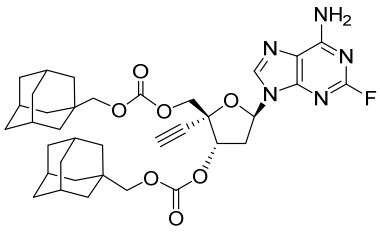
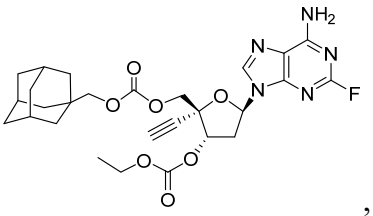
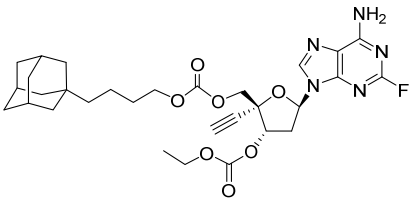
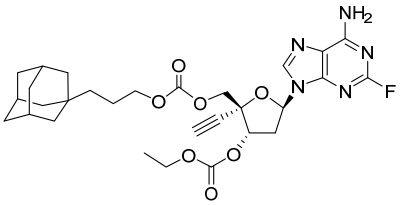
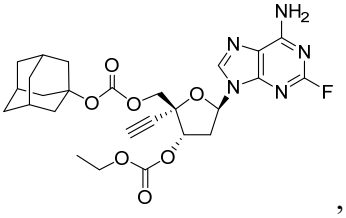
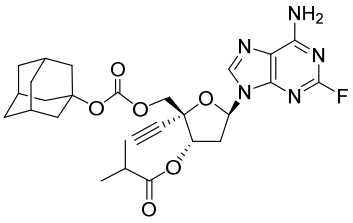
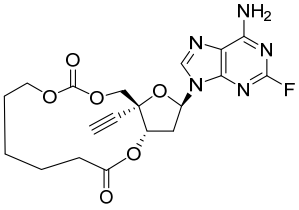
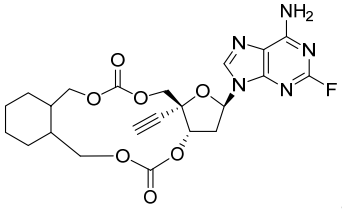
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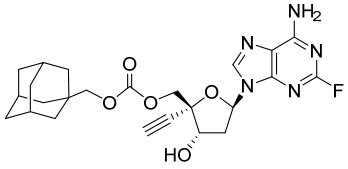
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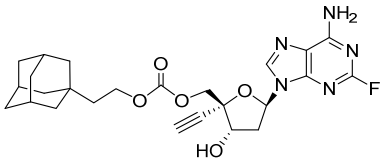

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and a pharmaceutically acceptable salt, tautomer, or solvate thereof.

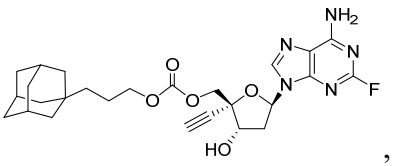
29. The adenosine derivative or pharmaceutically acceptable salt of claim 1, which is


, or a pharmaceutically acceptable salt thereof.

30. The adenosine derivative or pharmaceutically acceptable salt of claim 1, which is


, or a pharmaceutically acceptable salt thereof.

31. The adenosine derivative or pharmaceutically acceptable salt of claim 1, which is


, or a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition comprising an adenosine derivative or pharmaceutically acceptable salt of any one of claims 1-31 and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition of claim 32, wherein the pharmaceutical composition is suitable for oral administration.

34. The pharmaceutical composition of claim 32, wherein the pharmaceutical composition is suitable for parenteral administration.

35. The pharmaceutical composition of claim 34, wherein the pharmaceutical composition is a long-acting injectable composition.

36. The pharmaceutical composition of claim 34 or 35, wherein the pharmaceutical composition is suitable for intramuscular or subcutaneous injection.

37. The pharmaceutical composition of any one of claims 32-36, wherein the pharmaceutical composition is a liquid dosage form.

38. The pharmaceutical composition of any one of claims 32-36, wherein the pharmaceutical composition is a solid dosage form.

39. The pharmaceutical composition of claim 38, wherein the solid dosage form is a tablet.

40. The pharmaceutical composition of any one of claims 32-39, wherein the pharmaceutically acceptable carrier comprises polyethylene glycol (PEG), sulfobutylether b-cyclodextrin (SRBCD), 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.

41. The pharmaceutical composition of claim 40, wherein the pharmaceutically acceptable carrier comprises polyethylene glycol 400.

42. The pharmaceutical composition of any one of claims 32-41, further comprising one or more additional antiviral agents selected from lenacapavir, atazanavir, atazanavir sulfate, bictegravir, cabotegravir, darunavir, dolutegravir, doravirine, efavirenz, tenofovir disoproxil fumarate, tenofovir alafenamide, etravirine, a combination of darunavir and cobicistat, maraviroc, rilpivirine, and MK-8507.

43. The pharmaceutical composition of claim 42, wherein the antiviral agent is lenacapavir or cabotegravir.

44. The pharmaceutical composition of any one of claims 32-43 for use in therapy.

45. Use of the adenosine derivative or pharmaceutically acceptable salt of any one of claims1-31 in the manufacture of a pharmaceutical composition for treating or preventing an HIV infection, wherein an effective dosage of the pharmaceutical composition is to be administered to a subject in need thereof.

46. The use of claim45, 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.

47. The use of claim 45 or 46, wherein the administration is by oral administration.

48. The use of claim 45 or 46, wherein the administration is by parenteral administration.

49. The use of claim 48, wherein the parenteral administration is by intramuscular or subcutaneous injection.

50. The use of any one of claims 45-49, wherein the administration of the pharmaceutical composition results in a long-lasting plasma concentration of EFdA when compared to administration of a dose-equivalent EFdA under the same condition.

51. The use of any one of claims 45-49, 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.

52. The use of claim 51, wherein the administration of the pharmaceutical composition results in at least about 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.

53. The use of any one of claims45-49, 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.

54. The use of any one of claims 45-53, 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.

55. The use of claim 54, wherein the administration of the pharmaceutical composition results in at least about a 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.

56. The use of any one of claims 45-49, 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.

57. The use of claim 56, wherein the administration of the pharmaceutical composition results in at least about 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.

58. The use of any one of claims 45-57, wherein the pharmaceutical composition is to be administered in combination with one or more additional antiviral agent selected from lenacapavir, atazanavir, atazanavir sulfate, bictegravir, cabotegravir, darunavir, dolutegravir, doravirine, efavirenz, tenofovir disoproxil fumarate, tenofovir alafenamide, etravirine, a combination of darunavir and cobicistat, rilpivirine, MK-8507or a combination thereof.

59. The use of claim 58, wherein the one or more additional antiviral agent is lenacapavir, cabotegravir, or their prodrugs.