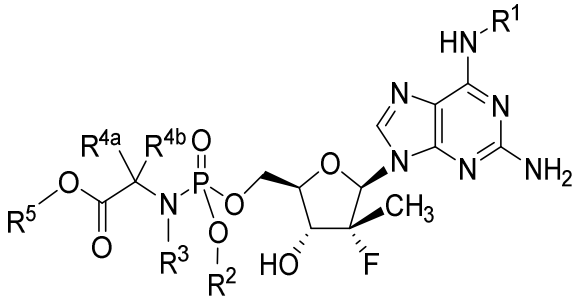
CLAIMS

What is claimed is:

1. Use of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for use to treat COVID-19 caused by the SARS-CoV-2 in a human in need thereof wherein:

R^1 is selected from C_1-C_6alkyl, C_3-C_6cycloalkyl, and -C(O)C_1-C_6alkyl;

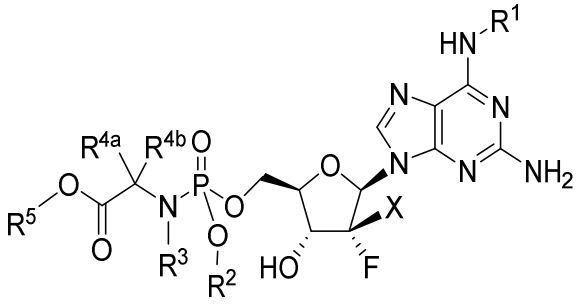
R^2 is hydrogen, C_1-$_6$alkyl, C_3-$_7$cycloalkyl, aryl, aryl(C_1-C_4alkyl)-, heteroaryl, or heteroalkyl;

R^3 is hydrogen or C_1-$_6$alkyl;

R^{4a} and R^{4b} are independently selected from hydrogen, C_1-$_6$alkyl, and C_3-$_7$cycloalkyl; and

R^5 is hydrogen, C_1-$_6$alkyl, C_1-$_6$haloalkyl, C_3-$_7$cycloalkyl, aryl(C_1-C_4alkyl)-, aryl, heteroaryl, or heteroalkyl.

2. Use of a compound of Formula III:



Formula III

or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for use to treat COVID-19 caused by the SARS-CoV-2 virus in a human in need thereof wherein:

X is selected from C_1-C_3haloalkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, and C_1-C_3hydroxyalkyl;

R^1 is selected from C_1-C_6alkyl, C_3-C_6cycloalkyl, and -C(O)C_1-C_6alkyl;

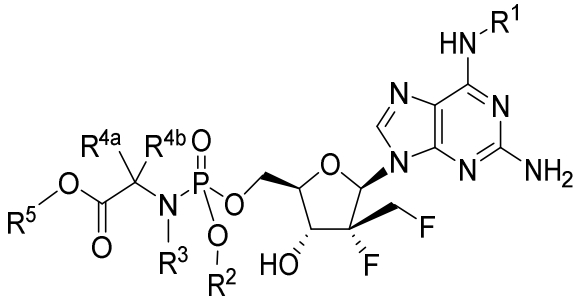
R^2 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, aryl(C_1-C_4alkyl)-, heteroaryl, or heteroalkyl;

R^3 is hydrogen or C_{1-6}alkyl;

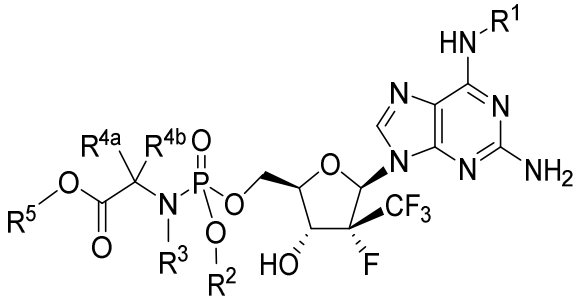
R^{4a} and R^{4b} are independently selected from hydrogen, C_{1-6}alkyl, and C_{3-7}cycloalkyl; and

R^5 is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, aryl(C_1-C_4alkyl)-, aryl, heteroaryl, or heteroalkyl.

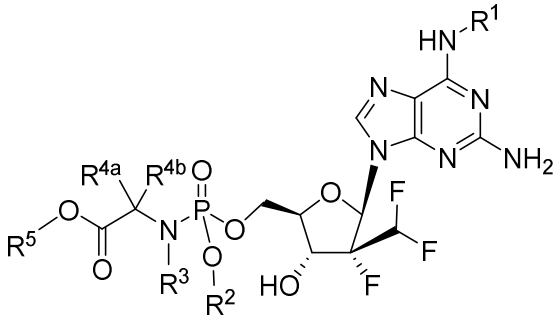
3. The use of claim 2, wherein the compound is selected from Formula IIIa, Formula IIIb, Formula IIIc, Formula IIId, Formula IIIe, and Formula IIIf :



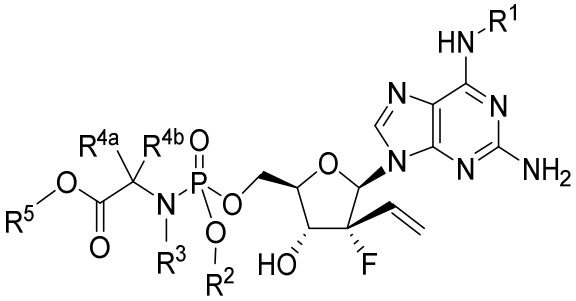
Formula IIIa



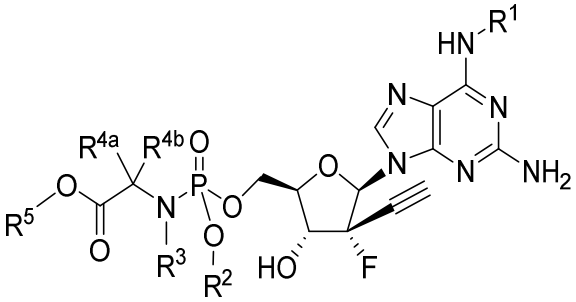
Formula IIIb



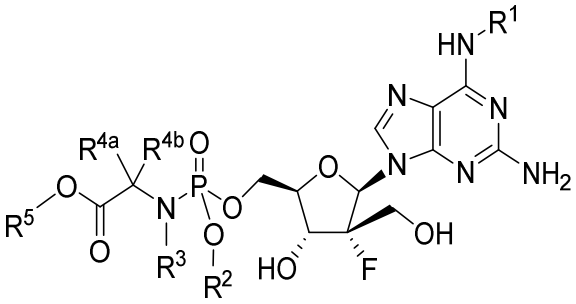
Formula IIIc



Formula IIId



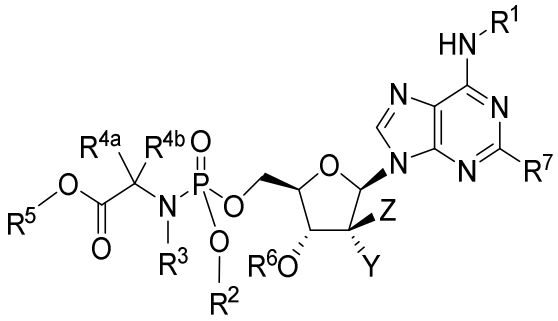
Formula IIIe



Formula IIIf

or a pharmaceutically acceptable salt thereof.

4. Use of a compound of Formula VI:



Formula VI

or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for use to treat COVID-19 caused by the SARS-CoV-2 virus in a human in need thereof wherein

R^1 is selected from C_1-C_6alkyl, C_3-C_6cycloalkyl, and -C(O)C_1-C_6alkyl;

R^2 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, aryl(C_1-C_4alkyl)-, heteroaryl, or heteroalkyl;

R^3 is hydrogen or C_{1-6}alkyl;

R^{4a} and R^{4b} are independently selected from hydrogen, C_{1-6}alkyl, and C_{3-7}cycloalkyl;

R^5 is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, aryl(C_1-C_4alkyl)-, aryl, heteroaryl, or heteroalkyl;

R^6 is selected from hydrogen, -C(O)R^{6A}, -C(O)OR^{6A}, C_{1-6}alkyl, -CH_2-O-R^{6A};

R^{6A} is selected from hydrogen, C_{1-6}alkyl, C_1-C_6haloalkyl, aryl, aryl(C_{1-6}alkyl)- wherein the aryl group is optionally substituted with a substituent selected from alkoxy, hydroxy, nitro, bromo, chloro, fluoro, azido, and haloalkyl;

R^7 is NH_2, H, or -N$R^8$$R^9$;

R^8 and R^9 are independently selected from hydrogen, C_{1-6}alkyl, -C(O)R^{6A}, and -C(O)OR^{6A};

Y is selected from F and Cl; and

Z is selected from methyl, C_1-C_3haloalkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_3hydroxyalkyl, and halogen.

5. The use of any one of claims 1-4, wherein R^2 is aryl.

6. The use of claim 5, wherein R^2 is phenyl.

7. The use of any one of claims 1-6, wherein R^3 is hydrogen.

8. The use of any one of claims 1-6, wherein R^3 is methyl.

9. The use of any one of claims 1-8, wherein R^{4a} is methyl and R^{4b} is hydrogen.

10. The use of any one of claims 1-8, wherein R^{4a} is methyl and R^{4b} is methyl.

11. The use of any one of claims 1-10, wherein R^5 is C_1-C_6alkyl.

12. The use of claims 11, wherein R^5 is selected from methyl, ethyl, and isopropyl.

13. The use of claim 12, wherein R^5 is isopropyl.

14. The use of any one of claims 1-4,
wherein:
R^2 is phenyl;
R^3 is hydrogen;
R^{4a} is methyl;
R^{4b} is hydrogen; and
R^5 is isopropyl.

15. The use of any one of claims 1-4,
wherein:
R^2 is phenyl;
R^3 is hydrogen;
R^{4a} is methyl;
R^{4b} is hydrogen;

R^5 is isopropyl; and

the phosphoramidate is in the S_p-configuration.

16. The use of any one of claims 1-4,

wherein:

R^2 is phenyl;

R^3 is hydrogen;

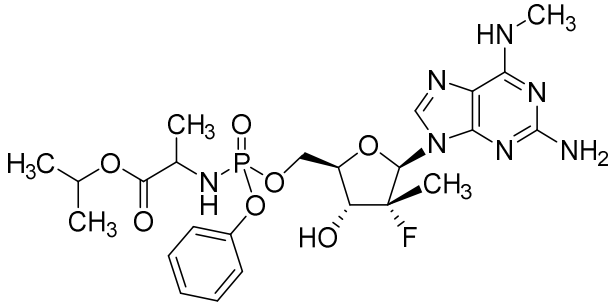
R^{4a} is methyl;

R^{4b} is hydrogen;

R^5 is isopropyl; and

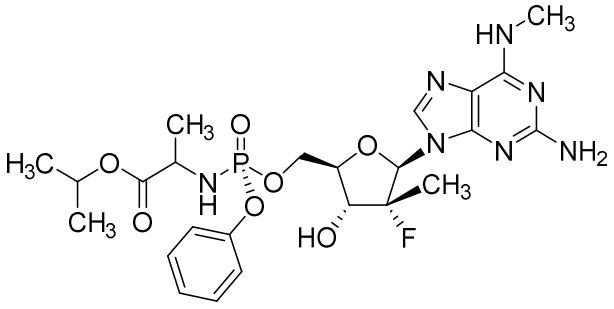
the phosphoramidate is in the R_p-configuration.

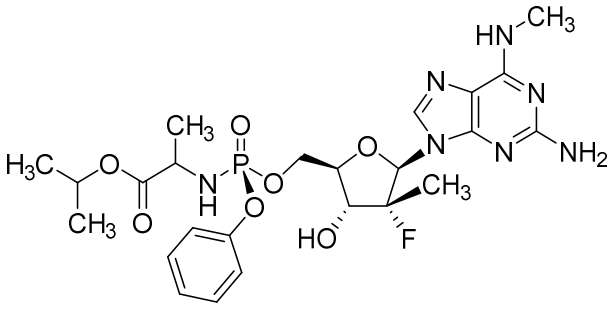
17. The use of claim 1, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

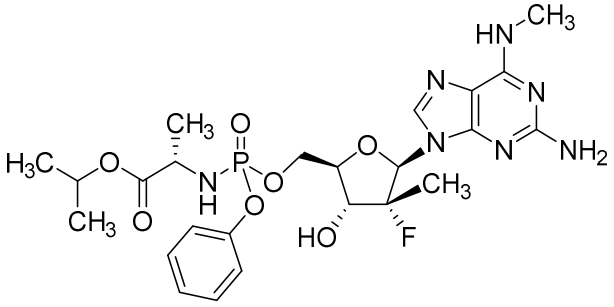
18. The use of claim 17, wherein the compound is selected from the formula:





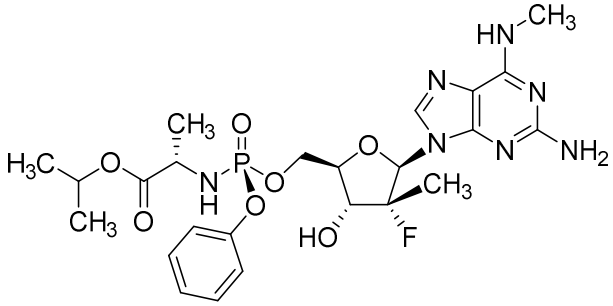
or a pharmaceutically acceptable salt thereof.

19. The use of claim 17, wherein the compound is of the formula:



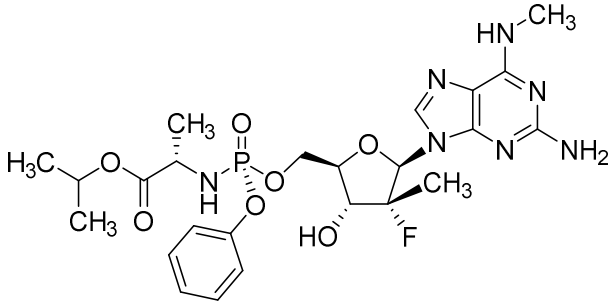
or a pharmaceutically acceptable salt thereof.

20. The use of claim 17, wherein the compound is of the formula:



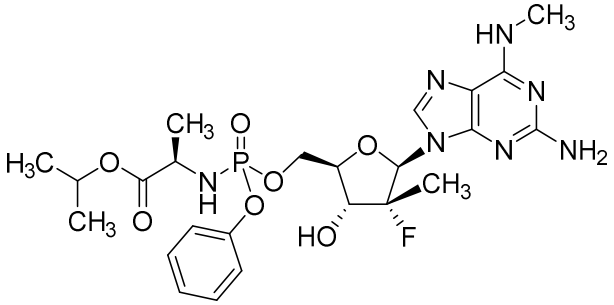
or a pharmaceutically acceptable salt thereof.

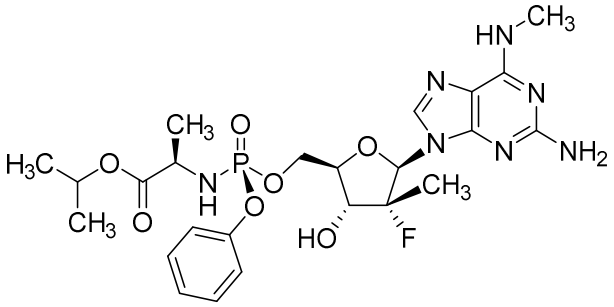
21. The use of claim 17, wherein the compound is of the formula:

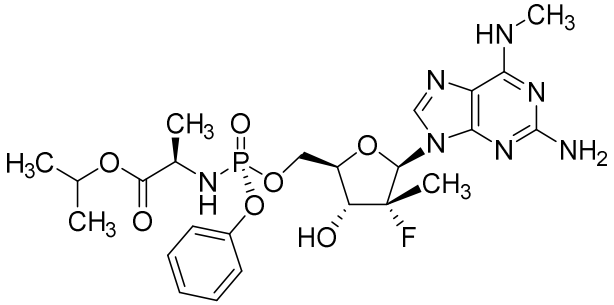


or a pharmaceutically acceptable salt thereof.

22. The use of claim 17, wherein the compound is selected from the formula:

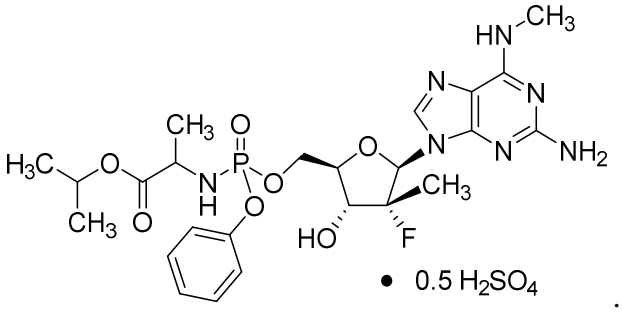




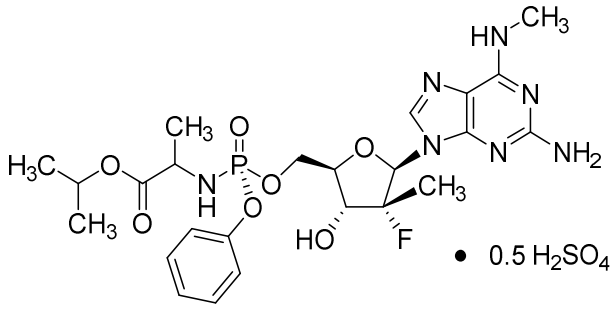


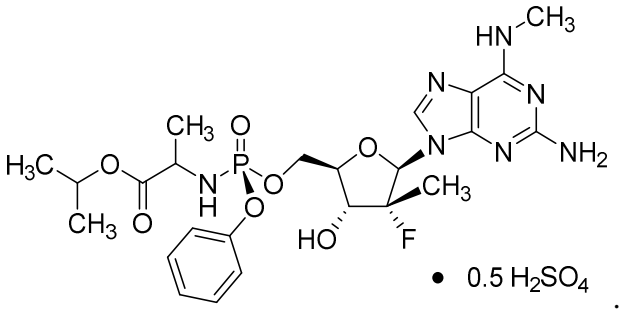
or a pharmaceutically acceptable salt thereof.

23. The use of claim 17, wherein the compound is of the formula:

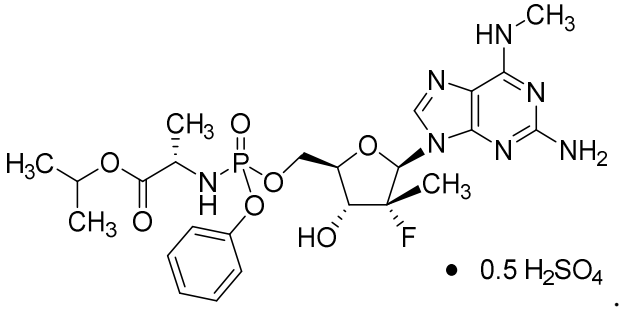


24. The use of claim 17, wherein the compound is selected from the formula:

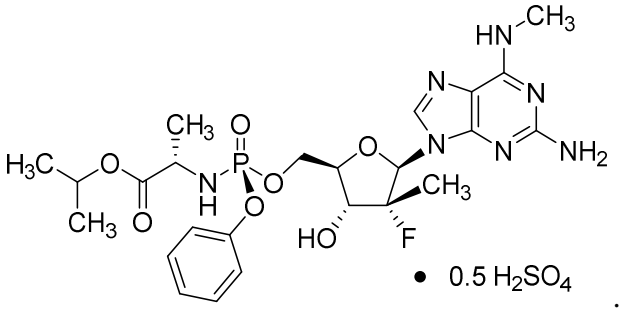




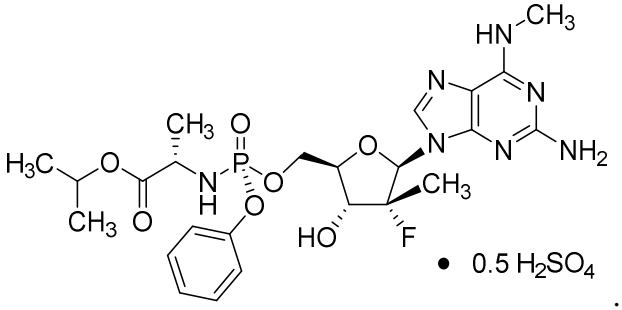
25. The use of claim 17, wherein the compound is of the formula:



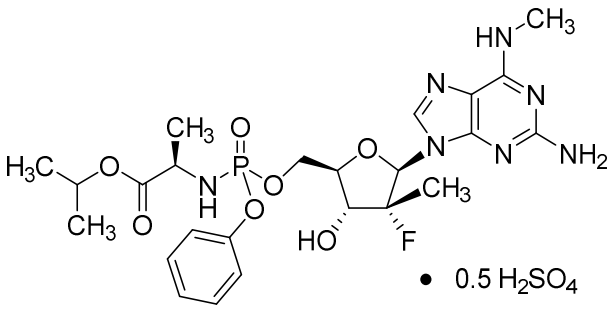
26. The use of claim 17, wherein the compound is of the formula:

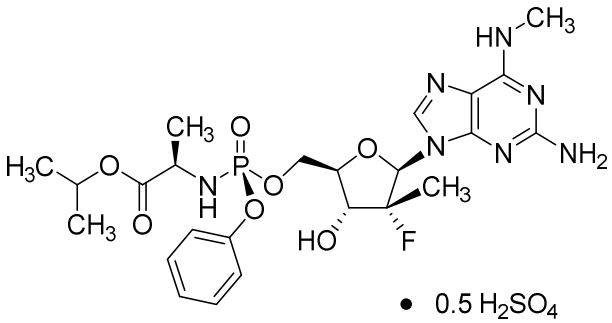


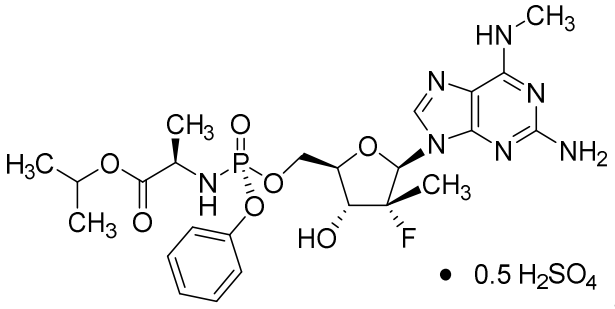
27. The use of claim 17, wherein the compound is of the formula:



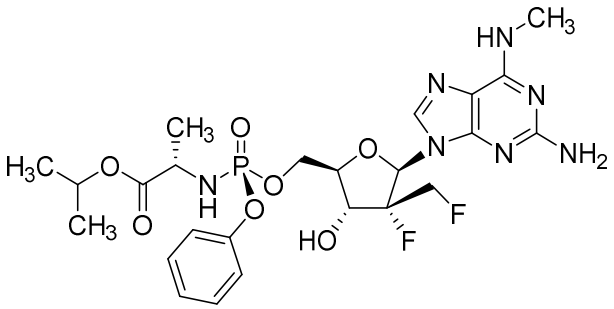
28. The use of claim 17, wherein the compound is selected from the formula:







29. The use of claim 3, wherein the compound is selected from:



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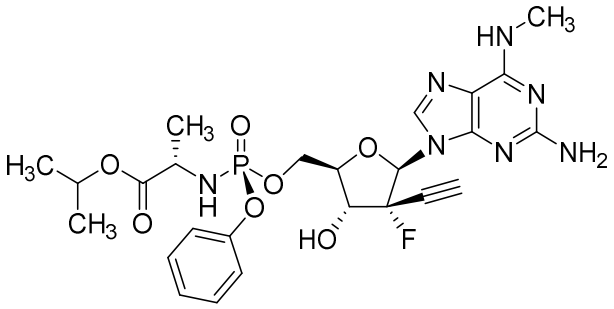

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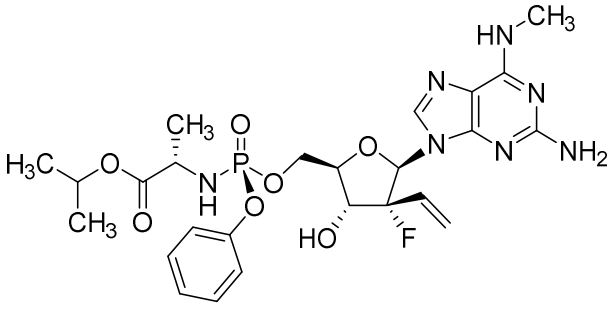

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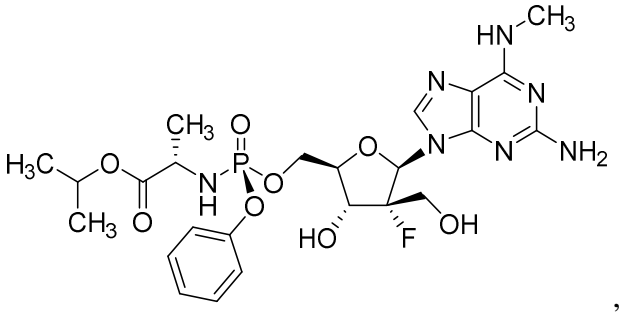

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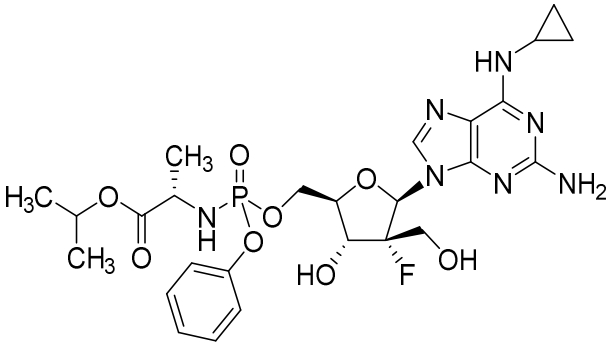
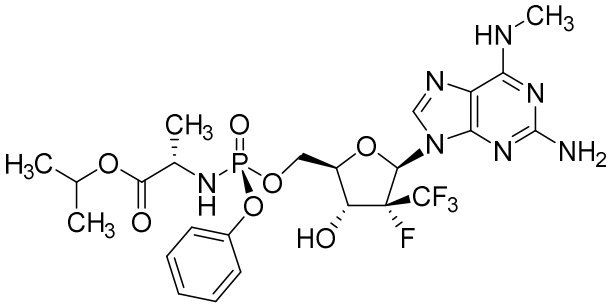
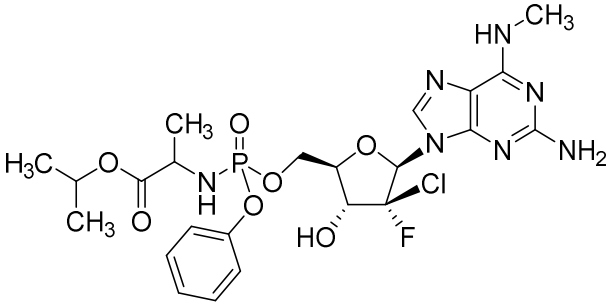


, and



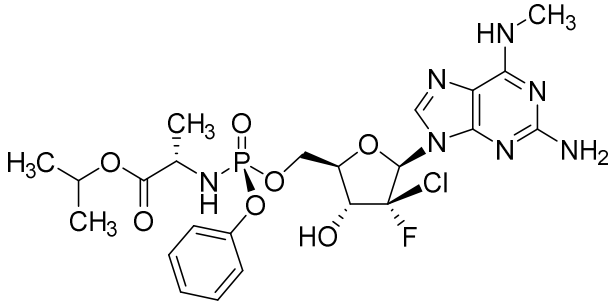
or a pharmaceutically acceptable salt thereof.

30. The use of claim 4, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

31. The use of claim 30, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

32. The use of any one of claims 1-31, wherein the medicament is in a dosage form suitable for oral administration.

33. The use of claim 32, wherein the dosage form is a solid dosage form.

34. The use of claim 33, wherein the solid dosage form is a tablet.

35. The use of claim 33, wherein the solid dosage form is a capsule.

36. The use of claim 32, wherein the dosage form is a liquid dosage form.

37. The use of claim 36, wherein the liquid dosage form is a solution or a suspension.

38. The use of any one of claims 1-31, wherein the medicament is in a dosage form suitable for intravenous administration.

39. The use of any one of claims 1-31, wherein the medicament is in a dosage form suitable for parenteral administration.

40. The use of any one of claims 1-39, wherein the medicament for administration for at least five days.

41. The use of any one of claims 1-39, wherein the medicament for administration for at least one week.

42. The use of any one of claims 1-39, wherein the medicament for administration for at least two weeks.

43. The use of any one of claims 1-39, wherein the medicament is for administration for at least one month.

44. The use of any one of claims 1-39, wherein the medicament is for administration for at least two months.

45. The use of any one of claims 1-44, wherein the medicament is for administration once a day.

46. The use of any one of claims 1-44, wherein the medicament is for administration twice a day.

47. The use of any one of claims 1-44, wherein the medicament is for administration three times a day.

48. The use of any one of claims 1-47, wherein the medicament comprises at least about 500 mg of the compound.

49. The use of any one of claims 1-47, wherein the medicament comprises at least about 600 mg of the compound.

50. The use of any one of claims 1-47, wherein the medicament comprises at least about 700 mg of the compound.

51. The use of any one of claims 1-47, wherein the medicament comprises at least about 800 mg of the compound.

52. The use of any one of claims 1-47, wherein the medicament comprises at least about 1000 mg of the compound.

53. The use of any one of claims 1-47, wherein the medicament comprises at least 1200 mg of the compound.

54. The use of any one of claims 1-47, wherein the medicament comprises at least about 1500 mg of the compound.

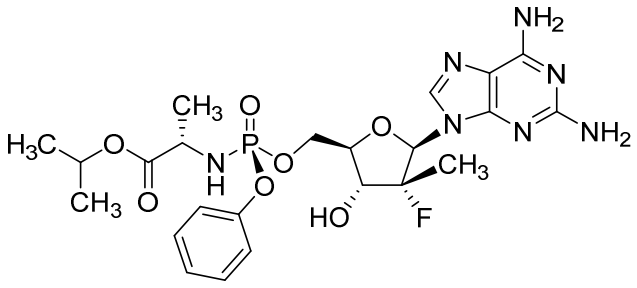
55. The use of any one of claims 1-47, wherein the medicament comprises at least about 550 mg of the compound and is for administration once a day.

56. The use of any one of claims 1-47, wherein the medicament comprises at least about 550 mg of the compound and is for administration twice a day.

57. The use of any one of claims 1-47, wherein the medicament comprises at least about 600 mg of the compound and is for administration once a day.

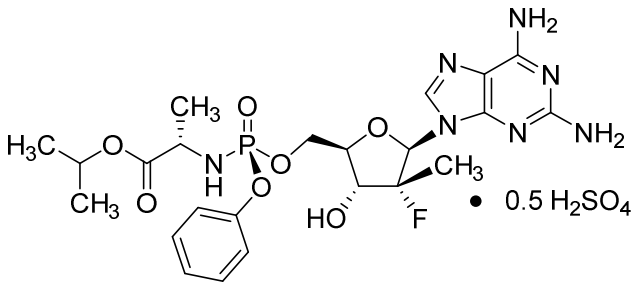
58. The use of any one of claims 1-47, wherein the medicament comprises at least about 600 mg of the compound and is for administration twice a day.

59. Use of a compound of the formula:



or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically carrier, in the manufacture of a medicament for use to treat COVID-19 caused by the SARS-CoV-2 virus in a human in need thereof wherein the medicament comprises about 550 mg of the compound and is for oral administration twice a day.

60. Use of a compound of the formula:



optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for use to treat COVID-19 caused by the SARS-CoV-2 virus in a human in need thereof, wherein the the medicament comprises about 600 mg of the compound and is for oral administration twice per day.

61. The use of claim 59 or 60, wherein the medicament is a tablet.

62. The use of claim 59 or 60, wherein the medicament is a capsule.

63. The use of any one of claims 59-62, wherein the medicament is for administration for at least five days.

64. The use of any one of claims 69-72, wherein the medicament is for administration for at least one week.

65. The use of any one of claims 69-72, wherein the medicament is for administration for at least two weeks.

66. The use of any one of claims 1-65, wherein the SARS-CoV-2 virus has developed a natural or drug-induced mutation.

67. The use of claim 66, wherein the natural or drug-induced mutation is in a viral protein selected from an envelope (E) protein, a membrane (M) protein, and a spike (S) protein.

68. The use of claim 67, wherein the mutation is in a spike (S) protein.

69. The use of claim 66, wherein the natural or drug-induced mutation is in a viral protein selected from nsp1, nsp2, nsp3, nsp4, nsp5, nsp 6, nsp7, nsp8, nsp9, nsp10, nsp12, nsp13, nsp14, nsp15, and nsp16.

70. The use of claim 66, wherein the natural or drug-induced mutation is in a viral protein selected from ORF1ab, ORF3a, ORF6, ORF7a, ORF7b, ORF8, and ORF10.