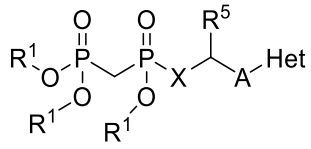
CLAIMS

1. A compound having the formula:



or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein,

each R^1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and $–C(R^2R^2)$-O-C(O)-OR^3, or two R^1 groups are optionally combined to form a 5- to 7-membered ring;

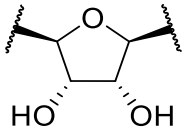
each R^2 is independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl;

each R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, and optionally substituted aryl;

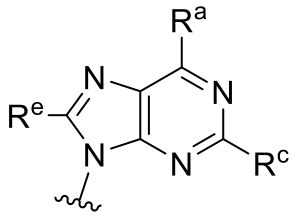
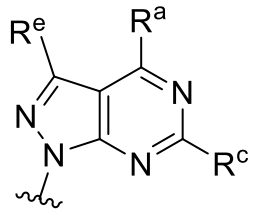
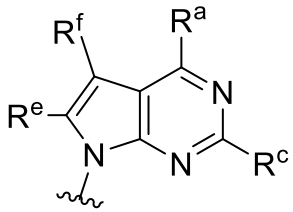
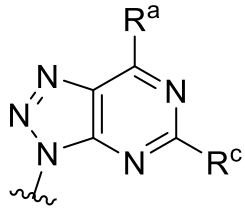
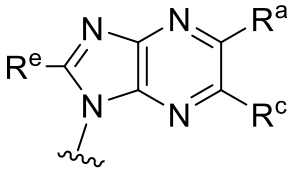
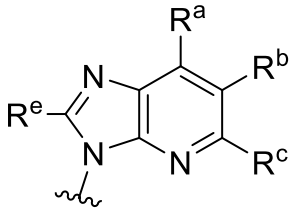
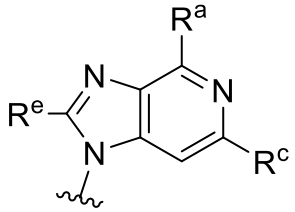
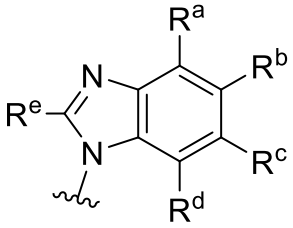
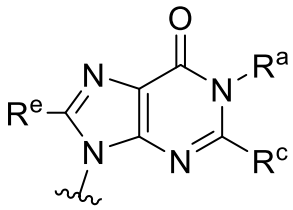
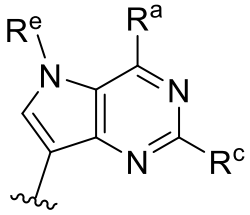
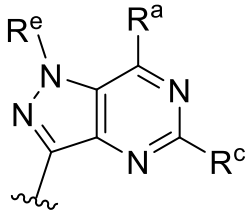
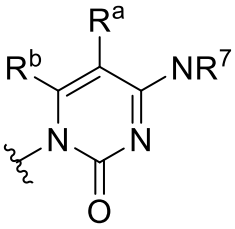
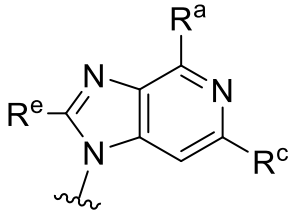
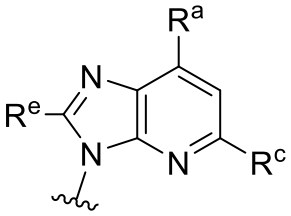
R^5 is selected from the group consisting of H and optionally substituted C_1-C_6 alkyl;

X is selected from the group consisting of O, CH_2, and S;

A is

 ; and

Het is selected from the group consisting of: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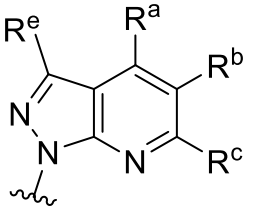


wherein the wavy line indicates the point of attachment to the remainder of the compound, and wherein:

R^a is selected from the group consisting of H, NH_2, NHR^7, $NHC(O)R^7$, NR^7R^7, R^7, OH, SR^7 and OR^7;

R^b is selected from the group consisting of H, halogen, NH_2, NHR^7, NR^7R^7, R^7, OH, and OR^7;

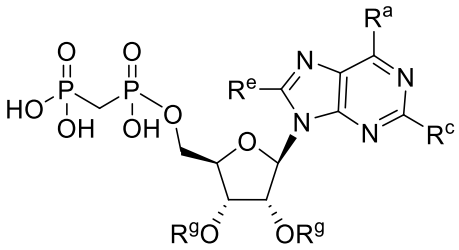
R^c and R^d are independently selected from the group consisting of H, halogen, haloalkyl, NH_2, NHR^7, NR^7R^7, R^7, OH, OR^7, SR^7, SO_2R^7, $-X^1-NH_2$, $-X^1-NHR^7$, $-X^1-NR^7R^7$, $-X^1-OH$, $-X^1-OR^7$, $-X^1-SR^7$ and $-X^1-SO_2R^7$;

R^e and R^f are independently selected from the group consisting of H, halogen, and optionally substituted C_1-C_6 alkyl;

each X^1 is C_1-C_4alkylene; and

each R^7 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_3-C_7 cycloalkylC_1-C_4alkyl, optionally substituted 4-7 membered cycloheteroalkyl, optionally substituted 4-7 membered cycloheteroalkylC_1-C_4alkyl, optionally substituted aryl, optionally substituted arylC_1-C_4alkyl, optionally substituted arylC_2-C_4alkenyl, optionally substituted arylC_2-C_4alkynyl, optionally substituted heteroaryl, optionally substituted heteroarylC_1-C_4alkyl, optionally substituted heteroarylC_1-C_4alkenyl, optionally substituted heteroarylC_2-C_4alkynyl, and optionally, two R^7 groups attached to a nitrogen atom are joined together to form a 4- to 7-membered heterocyclic ring, optionally fused to an aryl ring;

with the proviso that the compounds are other than those compounds wherein the combination of X, A, and Het results in



wherein R^g is H; and either

(i) R^c and R^e are hydrogen and R^a is -OEt, $-OCH_2Ph$, $-SCH_2Ph$, $-NH_2$, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, phenylamino, benzylamino, 1-phenylethylamino, 2-phenylethylamino, N-benzyl-N-ethylamino, N-benzyl-N-methylamino, dibenzylamino, 4-aminobenzylamino, 2-chlorobenzylamino, 3-chlorobenzylamino, 4-chlorobenzylamino, 4-hydroxybenzylamino, 4-methoxybenzylamino, 4-nitrobenzylamino, or 4-sulfamoylbenzylamino; or

(ii) R^c is hydrogen, R^a is $-NH_2$, and R^e is bromo, chloro, aminomethyl, or thioethyl; or

(iii) R^c is hydrogen, R^a is benzylamino, and R^e is bromo; or

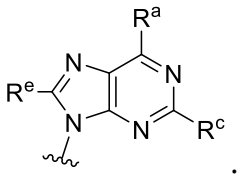
(iv) R^c is amino, R^e is hydrogen, and R^a is $–NH_2$, dimethylamino, diethylamino, benzylamino or N-benzyl-N-methylamino; or

(v) R^c is chloro, R^e is hydrogen, and R^a is $–NH_2$, benzylamino, 2-chlorobenzylamino, 1-phenylethylamino, (S)-1-phenylethylamino, (R)- 1-phenylethylamino or N-benzyl-N-methylamino; or

(vi) R^c is iodo, R^e is hydrogen, and R^a is $–NH_2$, benzylamino or N-benzyl-N-methylamino; or

(vii) R^a is amino, R^e is hydrogen, and R^c is piperazinyl, thioallyl or cyclohexylethylthio.

2. A compound of claim 1, wherein Het is:



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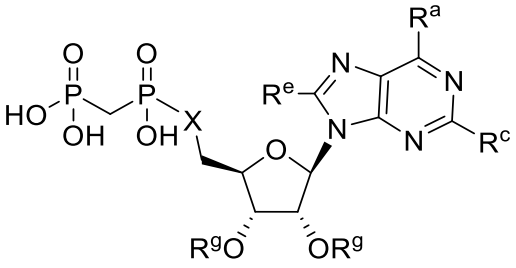
3. A compound of claim 2, wherein R^c is other than hydrogen.

4. A compound of claim 3, having a formula:



,

wherein each R^g is H.

5. A compound of claim 4, wherein X is oxygen.

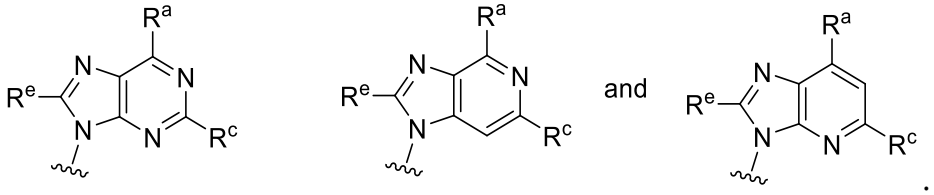
6. A compound of claim 5, wherein R^e is hydrogen.

7. A compound of claim 1, wherein R^5 is H.

8. A compound of claim 1, wherein R^5 is H, and X is O.

9. A compound of claim 1, wherein R^5 is H, X is O, and each R^1 is H.

10. A compound of claim 1, wherein Het is selected from

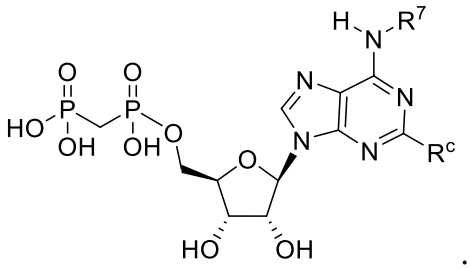


11. A compound of claim 2, wherein R^5 is H, X is O, and each R^1 is H.

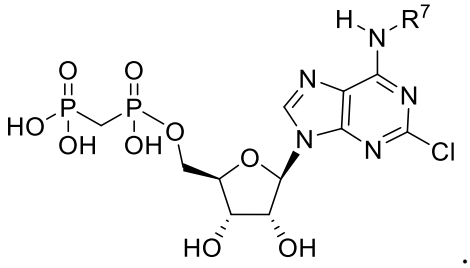
12. A compound of claim 10, wherein R^5 is H, X is O, each R^1 is H, R^e is H, and R^a is selected from the group consisting of NH_2, NHR^7 and $N(R^7)_2$.

13. A compound of claim 10, wherein R^5 is H, X is O, each R^1 is H, R^e is H, R^c is other than H, and R^a is NHR^7.

14. A compound of claim 4, having the formula:



15. A compound of claim 14, having the formula:



16. A compound of claim 1, selected from the compounds of Table 1.

17. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable excipient.

18**.** A combination comprising a compound of claim 1, and at least one additional therapeutic agent.

19. A combination of claim 18, wherein the at least one additional therapeutic agent is a chemotherapeutic agent, an immune- and/or inflammation-modulating agent, an anti-hypercholesterolemia agent, or an anti-infective agent.

20. A combination of claim 18, wherein the at least one additional therapeutic agent is an immune checkpoint inhibitor.

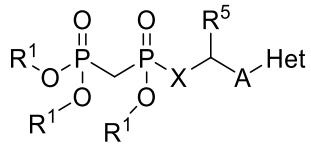
21. A kit comprising a compound of claim 1, and at least one additional therapeutic agent.

22. A kit of claim 21, wherein the at least one additional therapeutic agent is a chemotherapeutic agent, an immune- and/or inflammation-modulating agent, an anti-hypercholesterolemia agent, or an anti-infective agent.

23. A kit of claim 21, wherein the at least one additional therapeutic agent is an immune checkpoint inhibitor.

24. A combination, kit or method of claim 20 or claim 23, wherein said immune checkpoint inhibitor is selected from the group consisting of ipulimumab, nivolumab and lambrolizumab.

25. A compound having the formula:



or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein,

each R^1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, and $–C(R^2R^2)$-O-C(O)-OR^3, or two R^1 groups are optionally combined to form a 5- to 7-membered ring;

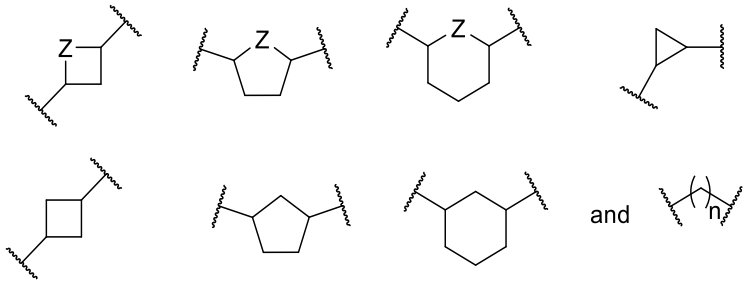
each R^2 is independently selected from the group consisting of H and optionally substituted C_1-C_6 alkyl;

each R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, and optionally substituted aryl;

R^5 is selected from the group consisting of H and optionally substituted C_1-C_6 alkyl;

X is selected from the group consisting of O, CH_2, and S;

A is selected from the group consisting of:

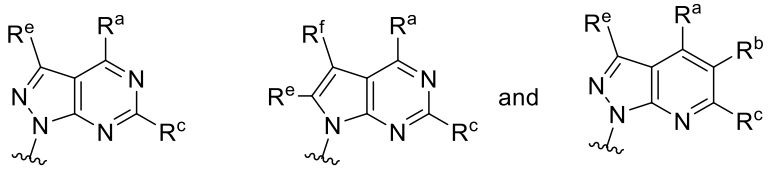


each of which is optionally substituted with from 1 to 5 R^6 substituents, and wherein the subscript n is an integer from 0 to 3;

Z is selected from the group consisting of CH_2, CHR^6, NR^6, and O;

each R^6 is independently selected from the group consisting of H, CH_3, OH, CN, F, optionally substituted C_1-C_6 alkyl, and OC(O)-C_1-C_6 alkyl; and optionally two R^6 groups on adjacent ring vertices are joined together to form a 5- to 6-membered ring having at least one heteroatom as a ring vertex; and

Het is selected from the group consisting of:



wherein the wavy line indicates the point of attachment to the remainder of the compound, and wherein:

R^a is selected from the group consisting of H, NH_2, NHR^7, $NHC(O)R^7$, NR^7R^7, R^7, OH, SR^7 and OR^7;

R^b is selected from the group consisting of H, halogen, NH_2, NHR^7, NR^7R^7, R^7, OH, and OR^7;

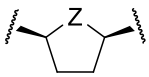
R^c is selected from the group consisting of H, halogen, haloalkyl, NH_2, NHR^7, NR^7R^7, R^7, OH, OR^7, SR^7, SO_2R^7, $-X^1-NH_2$, $-X^1-NHR^7$, $-X^1-NR^7R^7$, $-X^1-OH$, $-X^1-OR^7$, $-X^1-SR^7$ and $-X^1-SO_2R^7$;

R^e and R^f are independently selected from the group consisting of H, halogen, and optionally substituted C_1-C_6 alkyl;

each X^1 is C_1-C_4alkylene; and

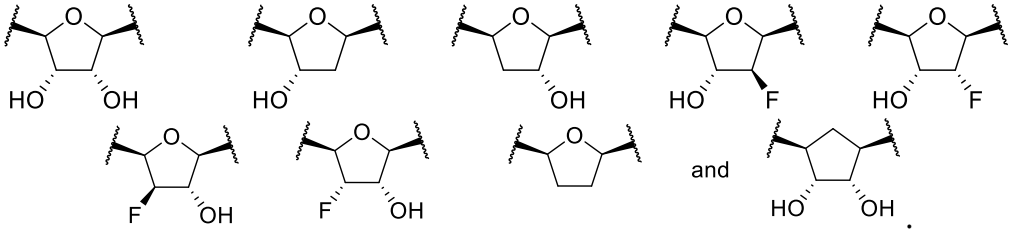
each R^7 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_3-C_7 cycloalkylC_1-C_4alkyl, optionally substituted 4-7 membered cycloheteroalkyl, optionally substituted 4-7 membered cycloheteroalkylC_1-C_4alkyl, optionally substituted aryl, optionally substituted arylC_1-C_4alkyl, optionally substituted arylC_2-C_4alkenyl, optionally substituted arylC_2-C_4alkynyl, optionally substituted heteroaryl, optionally substituted heteroarylC_1-C_4alkyl, optionally substituted heteroarylC_1-C_4alkenyl, optionally substituted heteroarylC_2-C_4alkynyl, and optionally, two R^7 groups attached to a nitrogen atom are joined together to form a 4- to 7-membered heterocyclic ring, optionally fused to an aryl ring.

26. A compound of claim 25, wherein A is:

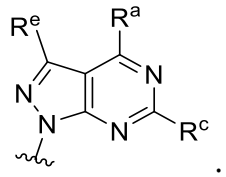


which is optionally substituted with from 1 to 5 R^6.

27. A compound of claim 26, wherein A is selected from the group consisting of:

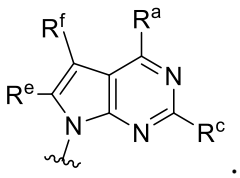


28. A compound of claim 25, wherein Het is



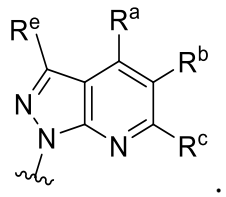
29. A compound of claim 28, wherein R^5 is H, X is O, each R^1 is H, R^e is H, R^c is other than H, and R^a is NHR^7.

30. A compound of claim 25, wherein Het is



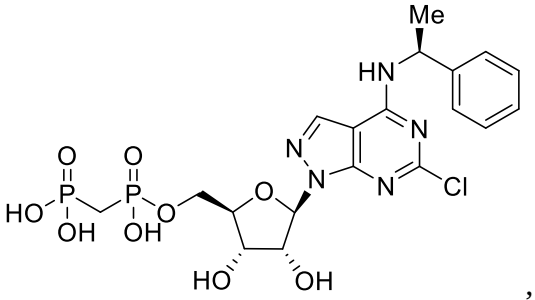
31. A compound of claim 30, wherein R^5 is H, X is O, each R^1 is H, R^e and R^f is H, R^c is other than H, and R^a is NHR^7.

32. A compound of claim 25, wherein Het is



33. A compound of claim 32, wherein R^5 is H, X is O, each R^1 is H, R^e and R^b is H, R^c is other than H, and R^a is NHR^7.

34. A compound of claim 26, selected from the group consisting of



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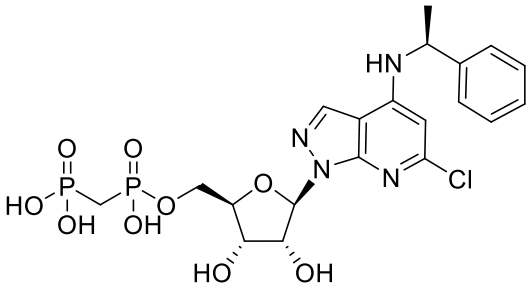

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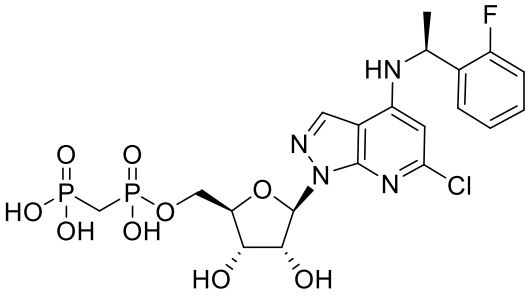

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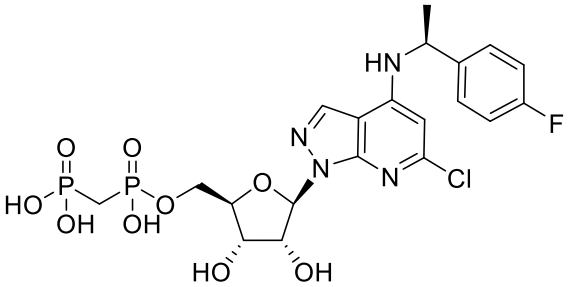

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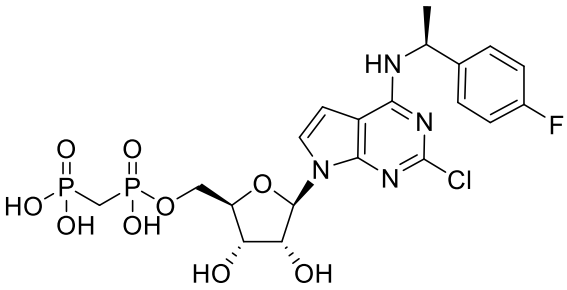

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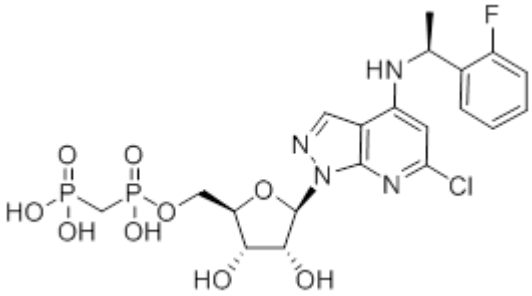
35. A compound of claim 26 or claim 34, having the formula:



or a pharmaceutically accepted salt thereof.