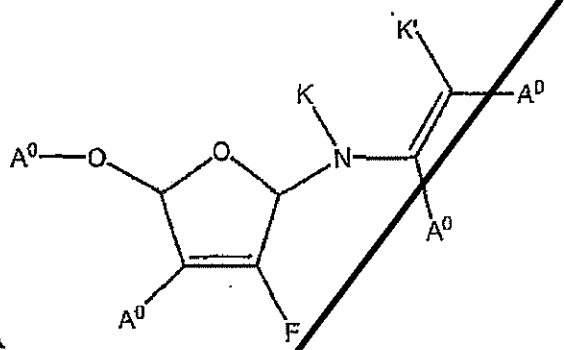
CLAIMS:

1. A conjugate comprising a compound that inhibits HIV linked to one or more phosphonate groups; or a pharmaceutically acceptable salt or solvate thereof.

2. The conjugate of claim 1, enantiomers thereof, or a pharmaceutically acceptable salt or solvate thereof, that is a compound of



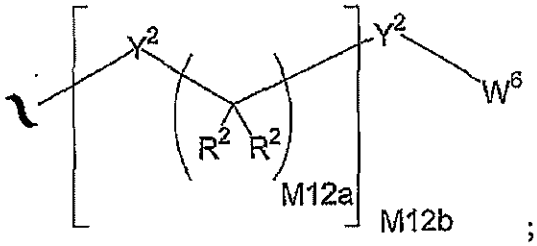
formula A

substituted with one or more groups A^0,

wherein:

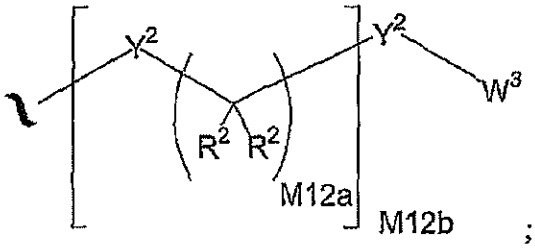
A^0 is A^1, A^2 or W^3 *with the proviso that the conjugate includes at least* one A^1;

A^1 is:



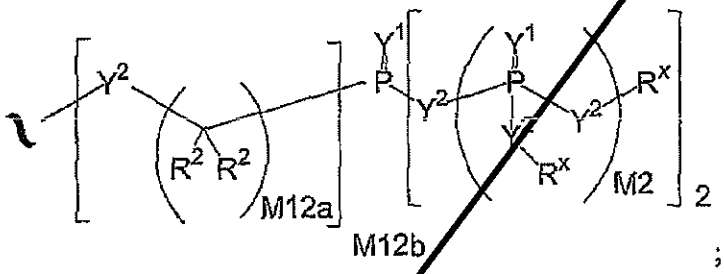
;

A^2 is:



;

A^3 is:

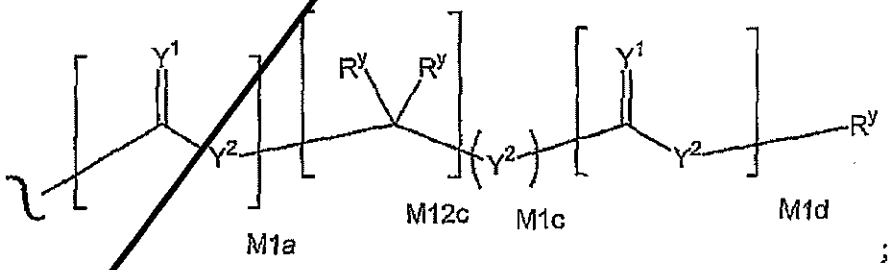


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently absent, a bond, O, $C(R^x)(R^x)$, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $S(O)_{M2}$-, or $-S(O)_{M2}-S(O)_{M2}$-; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^1, R^2, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3, $-NO_2$, $-OR_1$ or $-OR_{6a}$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 0, 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1;

K and K' are independently absent, a bond, or optionally substituted R^y; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

3. The conjugate of claim 2, or a pharmaceutically acceptable salt or solvate thereof, which has the formula:

$$[DRUG]\text{-}(A^0)_{nn}$$

wherein:

DRUG is a compound of formulae A; and

nn is 1, 2, or 3.

4. The conjugate of claim 2 which has any one of formulae A wherein: one A^0 is A^1;.

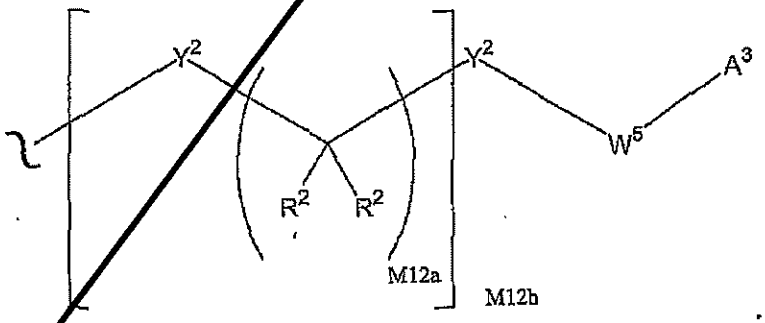
X^{61} is methoxy, ethoxy, propoxy, difluoromethoxy, trifluoromethoxy, vinyl, ethyl, methyl, propyl, butyl, cyclopropyl, N-methylamino, or N-formylamino;

X^{62} is methyl, chloro, or trifluoromethyl;

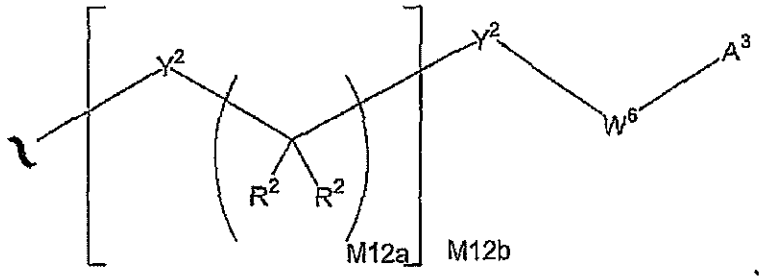
X^{63} is H, methyl, ethyl, cyclopropyl, vinyl, or trifluoromethyl; and

X^{64} is H, methyl, ethyl, cyclopropyl, chloro, vinyl, allyl, 3-methyl-1-buten-1yl.

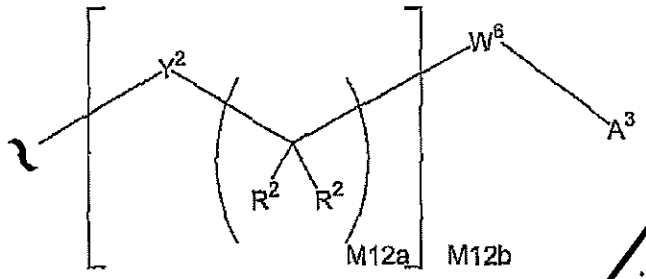
5. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



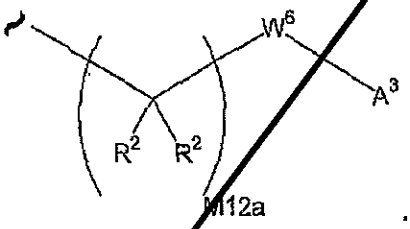
6. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



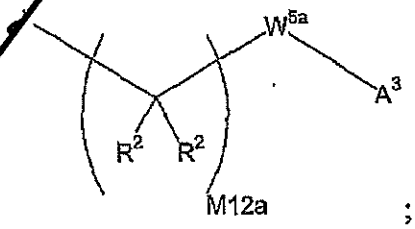
7. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



8. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



9. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:

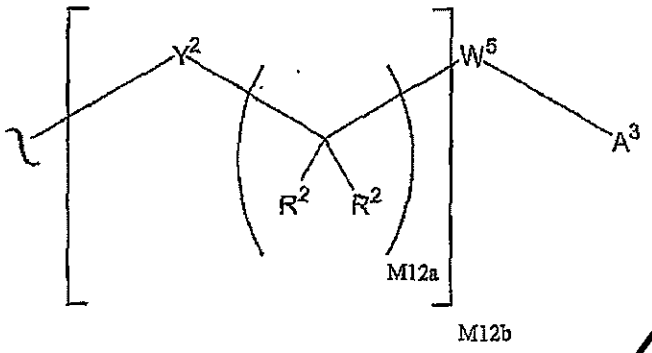


;

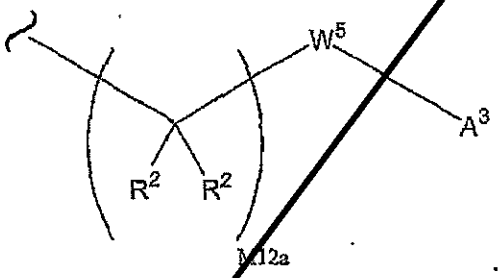
wherein: W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

10. The conjugate of any one of claims 2-4, wherein M12a is 1.

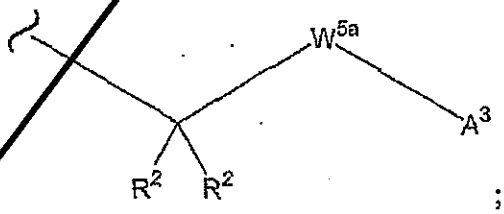
11. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



12. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



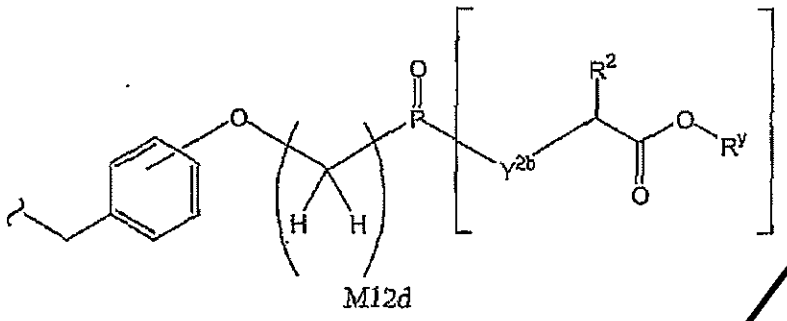
13. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



;

wherein: W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups.

14. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



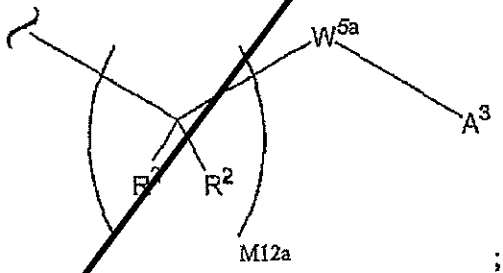
M12d

wherein:

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

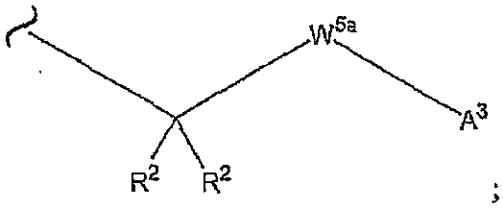
15. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



M12a ;

wherein: W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups.

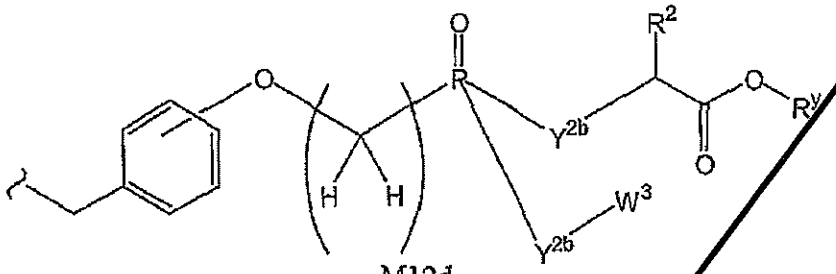
16. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



;

wherein: W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

17. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



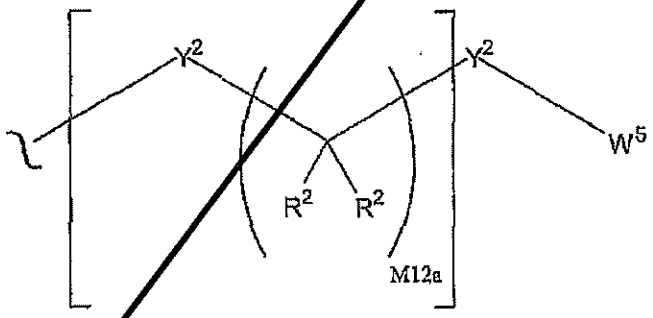
M12d

wherein:

Y^{2b} is O or $N(R^2)$; and

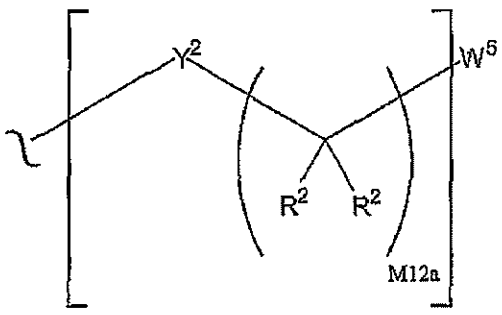
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

18. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:



M12b

19. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:

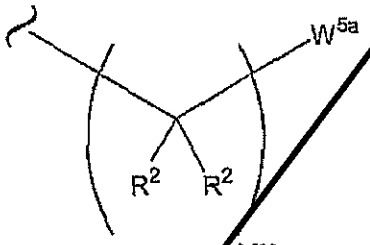


M12b.

20. The conjugate of any one of claims 2-17 wherein each M12b is 1.

21. The conjugate of claim 20 where M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

22. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:



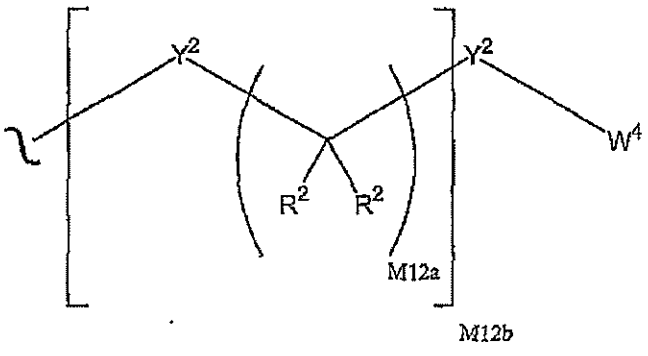
;

wherein: W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

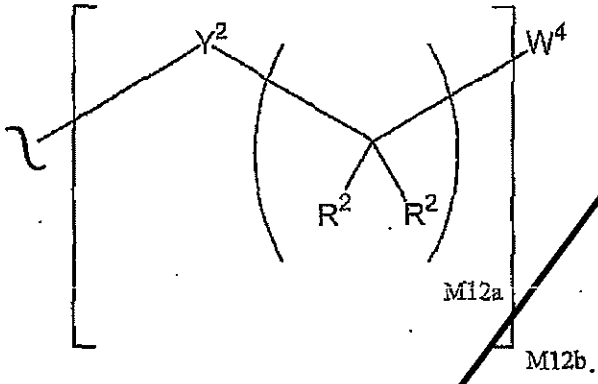
23. The conjugate of claim 22 wherein M12a is 1.

24. The conjugate of any one of claims 2-17 wherein each A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

25. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:

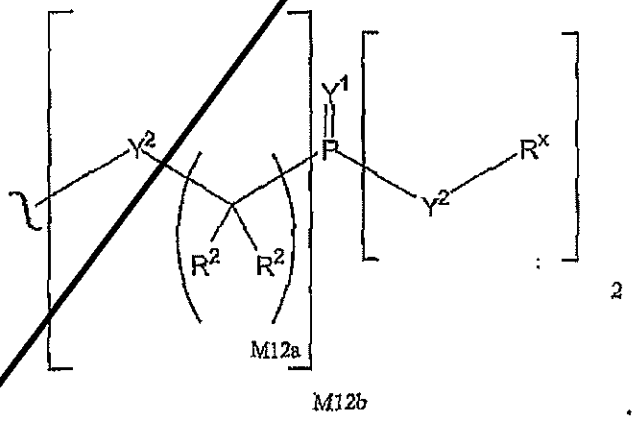


26. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:

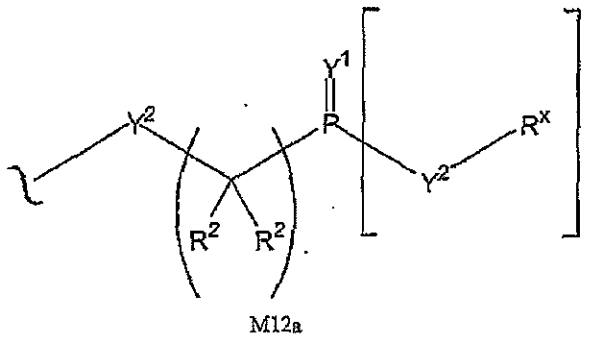


27. The conjugate of claim 26 wherein M12b is 1.

28. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

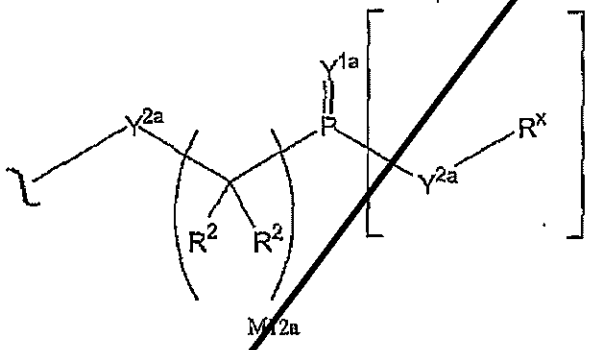


29. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12a

30. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



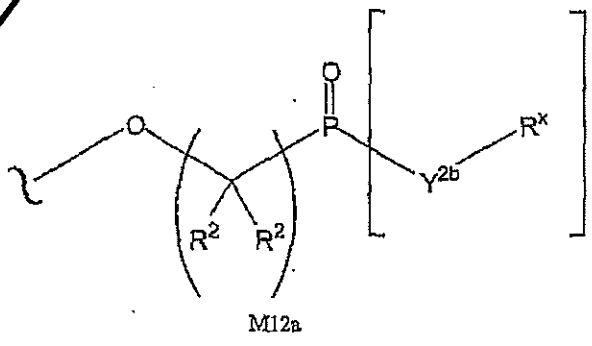
M12a ;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^x)$ or S.

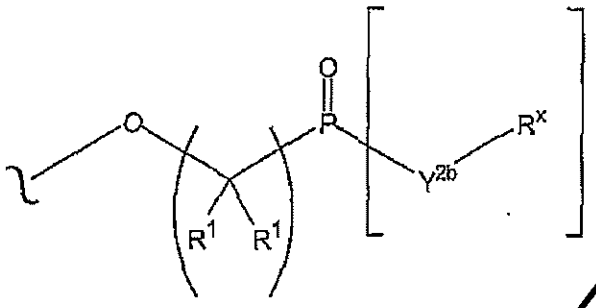
31. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12a ;

wherein Y^{2b} is O or $N(R^x)$.

32. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



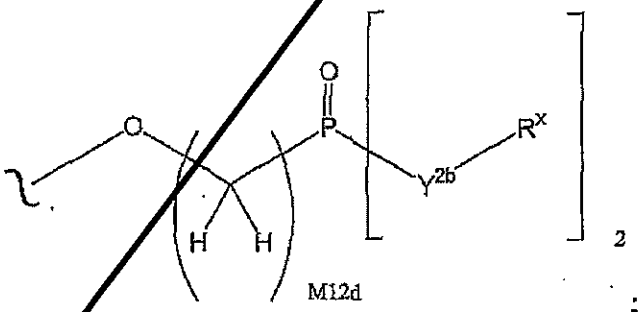
;

wherein:

Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

33. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



;

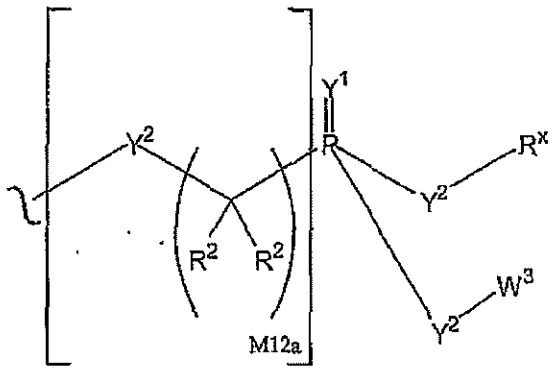
wherein:

Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

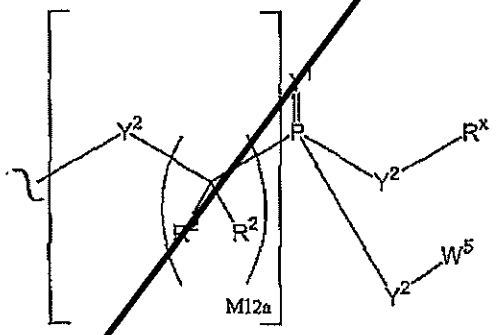
34. The conjugate of claim 33 wherein M12d is 1.

35. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12b

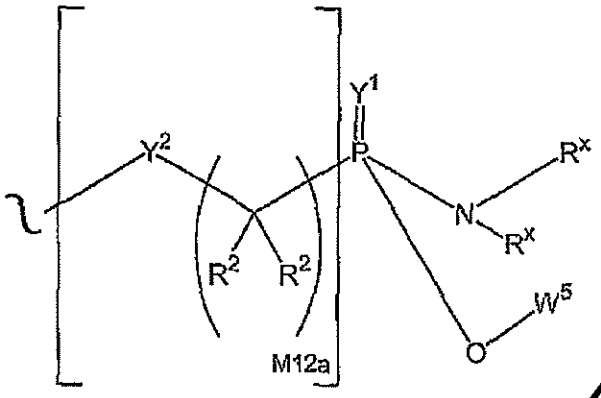
36. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12b

37. The conjugate of claim 36 wherein W^5 is a carbocycle.

38. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

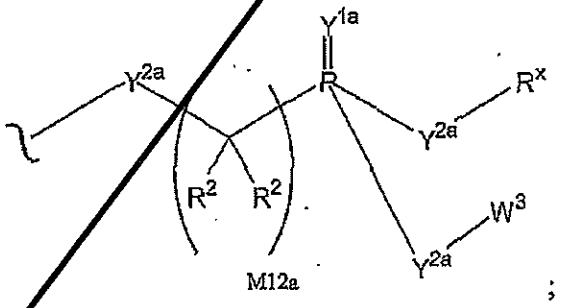


M12b

39. The conjugate of claim 38 wherein W^5 is phenyl.

40. The conjugate of claim 39 wherein M12b is 1.

41. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



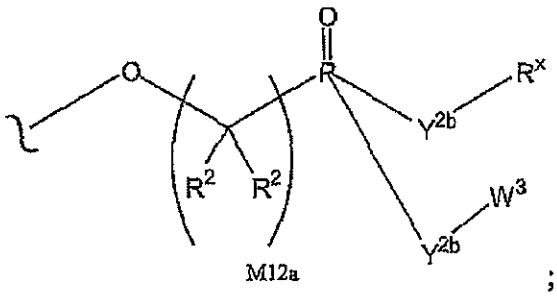
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, N(R^x) or S.

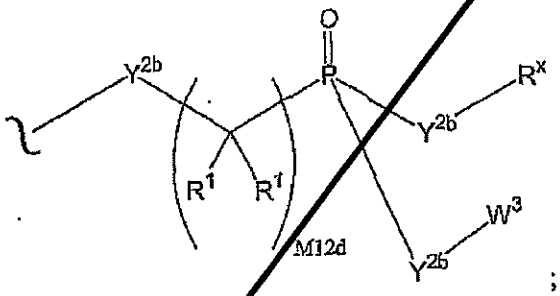
42. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12a ;

wherein Y^{2b} is O or $N(R^X)$.

43. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12d ;

wherein:

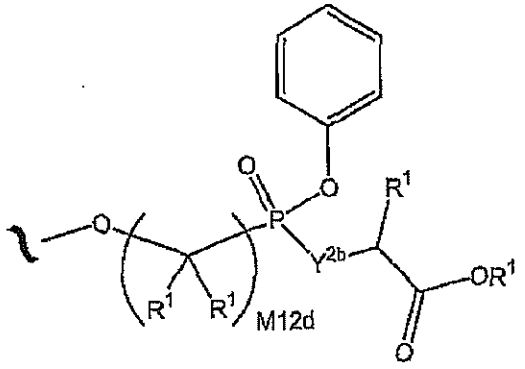
Y^{2b} is O or $N(R^X)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

44. The conjugate of claim 43 wherein R^1 is H.

45. The conjugate of claim 44 wherein M12d is 1.

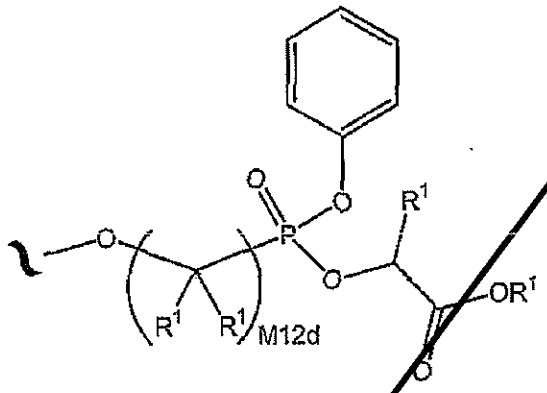
46. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12d

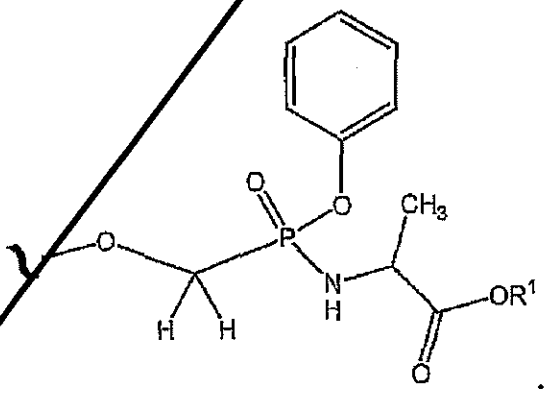
wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

47. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

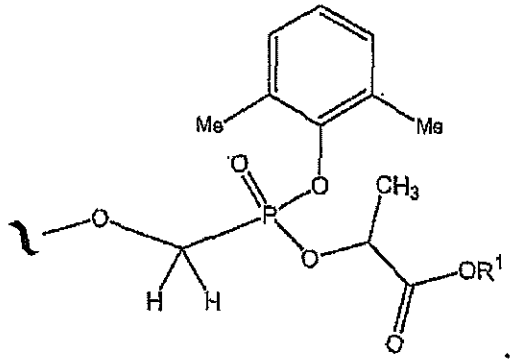


wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

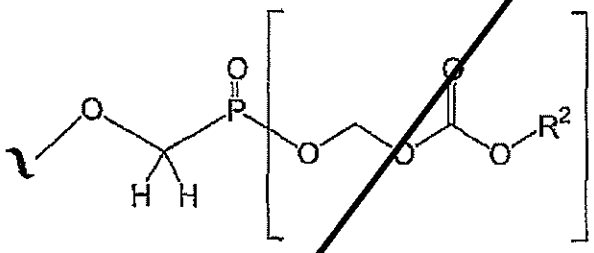
48. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



49. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

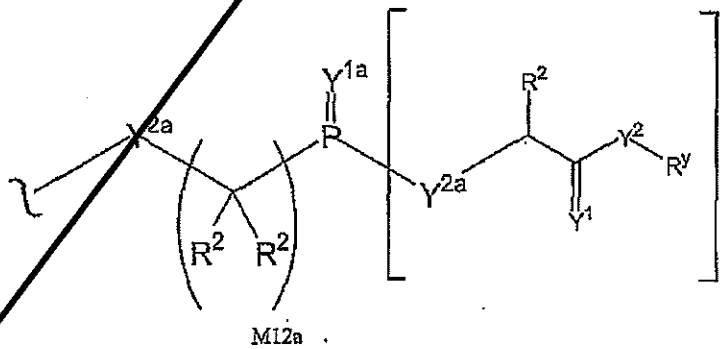


50. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



2.

51. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



2

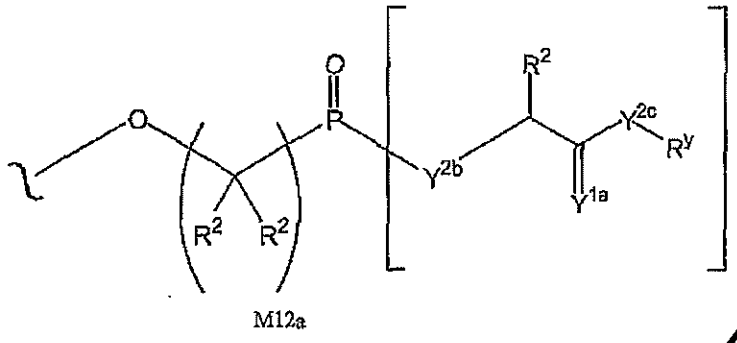
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

52. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12a ;

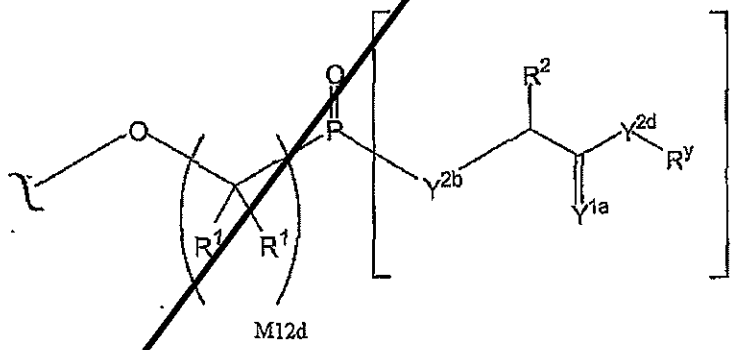
wherein:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

53. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12d 2

wherein:

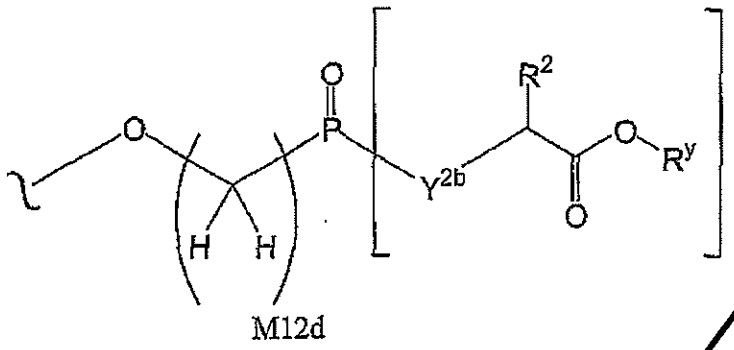
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

54. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12d

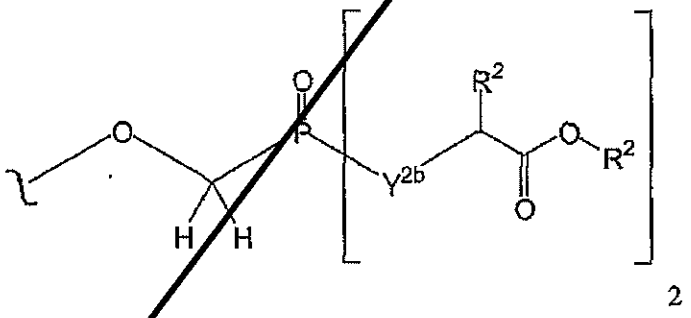
;

wherein:

Y^{2b} is O or $N(R^2)$; and

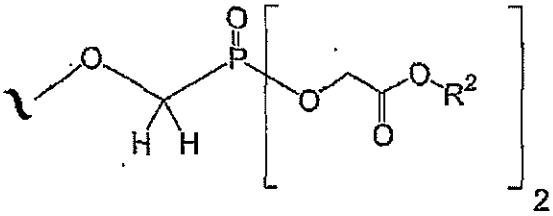
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

55. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

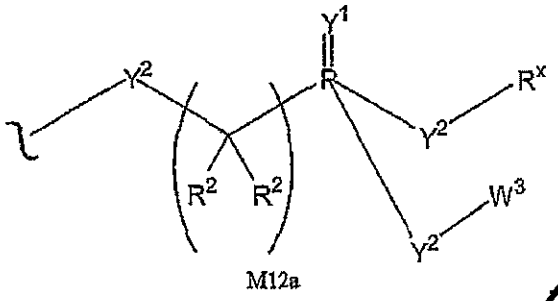


wherein Y^{2b} is O or $N(R^2)$.

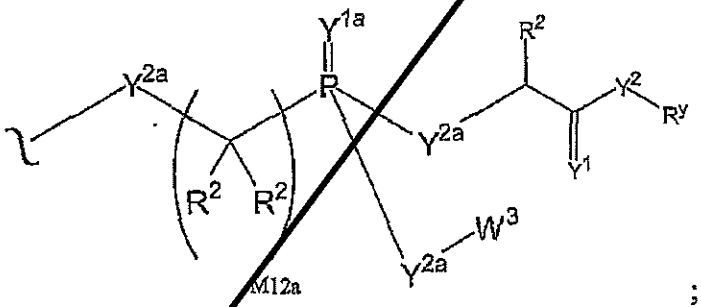
56. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



57. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



58. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



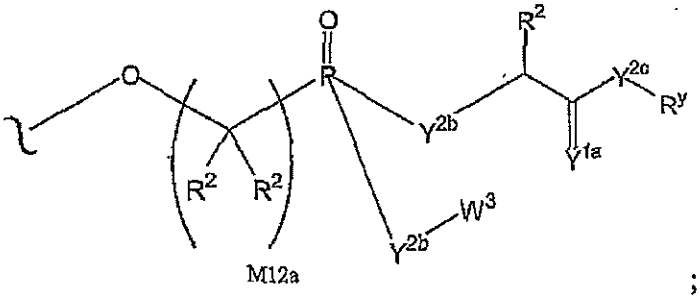
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, N(R^2) or S.

59. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



;

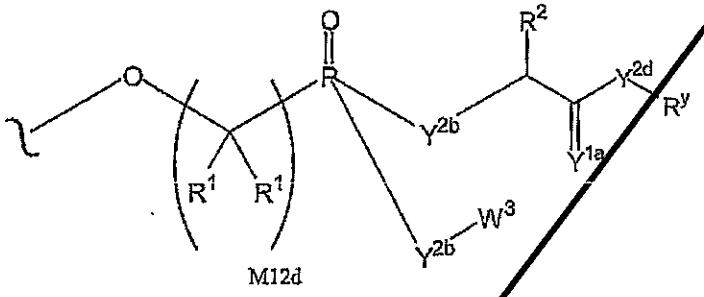
wherein:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

60. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



wherein:

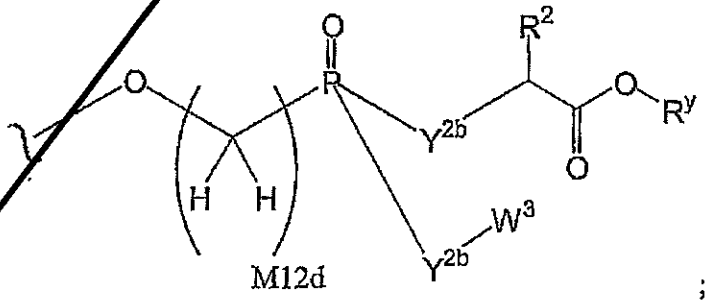
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

61. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



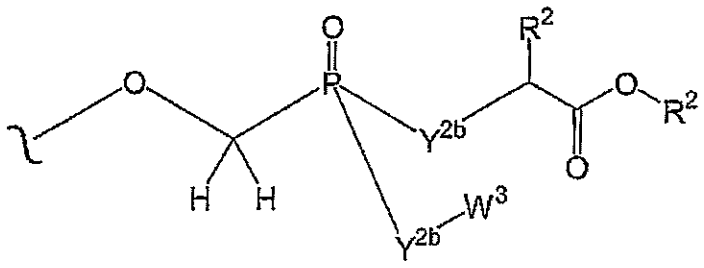
;

wherein:

Y^{2b} is O or $N(R^2)$; and

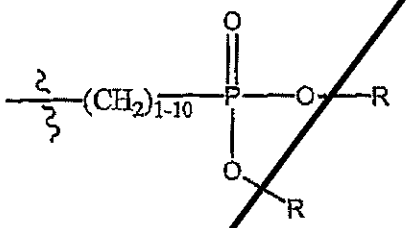
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

62. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



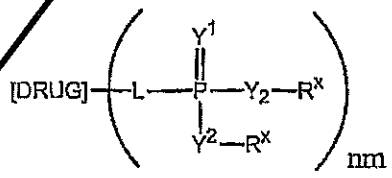
wherein Y^{2b} is O or $N(R^2)$.

63. The conjugate of claim 3 wherein A^0 is of the formula:



wherein each R is independently alkyl.

64. The conjugate of claim 1, 2, 3, or 4 which has the formula:



or a pharmaceutically acceptable salt or solvate thereof,

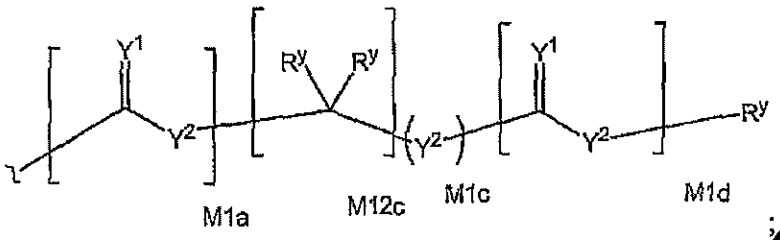
wherein:

DRUG is a compound that inhibits HIV;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^2, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3, $-NO_2$, $-OR_1$ or $-OR_{cl}$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 1, 2, or 3;

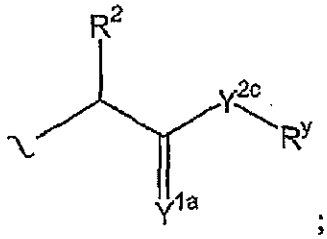
M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

nn is 1, 2, or 3; and

L is a direct bond or a linking group.

65. The conjugate of claim 64 wherein each R^x is of the formula:

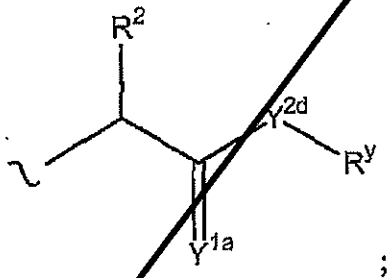


;

Y^{1a} is O or S; and

Y^{2c} is O, $N(R^y)$ or S.

66. The conjugate of claim 64 wherein each R^x is of the formula:

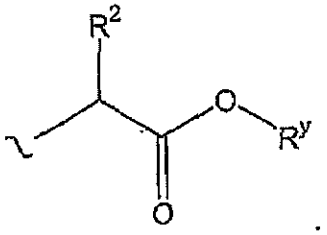


;

Y^{1a} is O or S; and

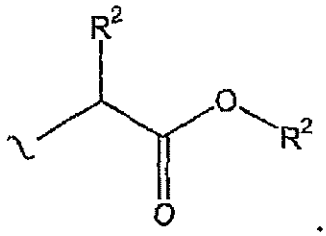
Y^{2d} is O or $N(R^y)$.

67. The conjugate of claim 64 wherein each R^x is of the formula:

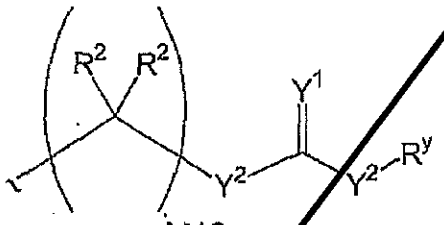


68. The conjugate of any one of claims 65-67 wherein each R^y is independently H or alkyl of 1 to 10 carbons.

69. The conjugate of claim 64 wherein each R^x is of the formula:

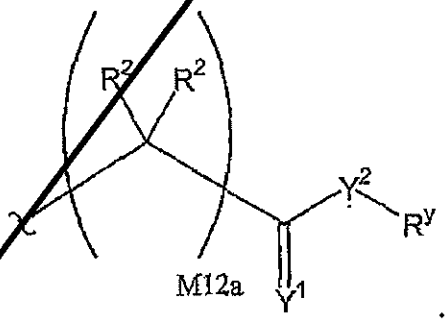


70. The conjugate of claim 64 wherein each R^x is of the formula:



M12a

71. The conjugate of claim 64 wherein each R^x is of the formula:



M12a

72. The conjugate of claim 64 wherein each Y^1 is O or S.

73. The conjugate of claim 64 wherein each Y^2 is O, $N(R^y)$ or S.

74. The conjugate of any one of claims 64-73 wherein nn is 1.

75. The conjugate of any one of claims 64-73 wherein nn is 2.

76. The conjugate of any one of claims 64-73 wherein nn is 3.

77. The conjugate of claim 64 wherein the compound that inhibits IMPDH is a compound of formula A.

78. The conjugate of claim 77 wherein each L has a molecular weight of from about 20 daltons to about 400 daltons.

79. The conjugate of claim 77 wherein each L has a length of about 5 angstroms to about 300 angstroms.

80. The conjugate of claim 77 wherein each L separates the compound of any one of formula A and the phosphorous of the phosphonate group by about 5 angstroms to about 200 angstroms, inclusive.

81. The conjugate of claim 77 wherein each L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more of the carbon atoms is optionally replaced by (-O-), and wherein the chain is optionally substituted on carbon with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

82. The conjugate of claim 77 wherein each L is of the formula W-A wherein A is (C_1-C_{24})alkylene, (C_2-C_{24})alkenylene, (C_2-C_{24})alkynylene, (C_3-C_8)cycloalkylene, (C_6-C_{10})aryl or a combination thereof, wherein each W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -$S(O)_2$-, -N(R)-, -C(=O)-, -N(R)C=N(R)-N(R)-, -C(R)=N(R)-, -$S(O)_{M2}$-N(R)-, -N(R)-$S(O)_{M2}$-, or a direct bond; wherein each R is independently H or alkyl of 1 to 10 carbons.

83. The conjugate of claim 82 wherein each A is alkylene of 1 to 10 carbons.

84. The conjugate of claim 77 wherein each L is a divalent radical formed from a peptide.

85. The conjugate of claim 77 wherein each L is a divalent radical formed from an amino acid.

86. The conjugate of claim 77 wherein each L is a divalent radical formed from poly-L-glutamic acid, poly-L-aspartic acid, poly-L-histidine, poly-L-ornithine, poly-L-serine, poly-L-threonine, poly-L-tyrosine, poly-L-leucine, poly-L-lysine-L-phenylalanine, poly-L-lysine or poly-L-lysine-L-tyrosine.

87. The conjugate of claim 77 wherein each L is of the formula W-$(CH_2)_n$ wherein, n is between about 1 and about 10; and W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(=O)-, -N(R)-, -N(R)C=N(R)-N(R)-, -C(R)=N(R)-, -$S(O)_{M2}$-N(R)-, -N(R)-$S(O)_{M2}$-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

88. The conjugate of claim 77 wherein each L is methylene, ethylene, or propylene.

89. The conjugate of claim 77 wherein each L is linked to P at a carbon atom of L.

90. The conjugate as described in any one of claims 1-89, which is isolated and purified.

91. An HIV inhibitor conjugate as described herein.

92. A compound of the formula MBF.

93. A compound of claim 92 selected from Table 100.

94. A pharmaceutical composition comprising a pharmaceutical excipient

and a conjugate as described in any one of claims 1-89 and 91-93.

95. A unit dosage form comprising a conjugate as described in any one of claims 1-89 and 91-93 and a pharmaceutical excipient.

96. A method for inhibiting 2 *in vitro* or *in vivo* comprising contacting a sample in need of such treatment with a conjugate as described in any one of claims 1-89 and 91-93.

97. The method of claim 96 wherein the contacting is *in vivo*.

98. The invention also provides a method of inhibiting HIV in a mammal, comprising administering a compound as described in any one of claims 1-89 and 91-93 to the mammal.

99. The method of claim 98 wherein the compound is formulated with a pharmaceutically acceptable excipient.

100. The method of claim 99 wherein the formulation further comprises a second active ingredient.

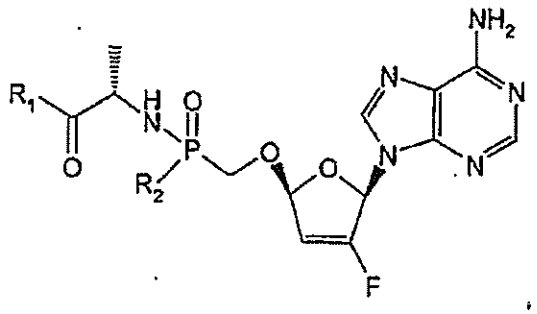
101. A compound as described in any one of claims 1-89 and 91-93 for use in medical therapy.

102. The use of a conjugate as described in any one of claims 1-89 and 91-93 to prepare a medicament for inhibiting HIV in an animal.

103. A method of preparing a compound or conjugate described herein according to the Examples or Schemes.

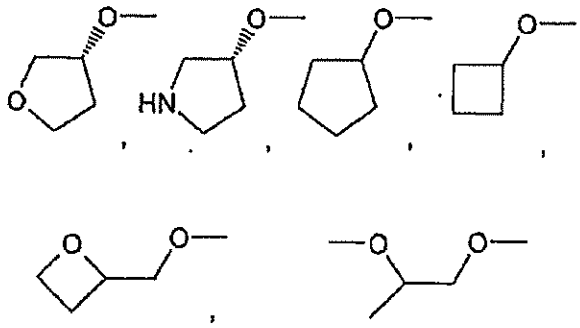
CLAIMS:

1. A compound of the formula

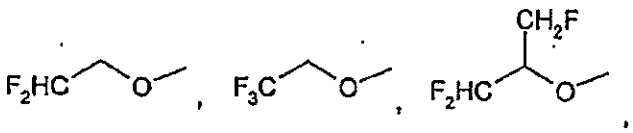


wherein

R_1 is



and
R_2 is



or a pharmaceutically acceptable salt or solvate thereof.

2. A pharmaceutical composition comprising a pharmaceutical excipient and a compound as described in claim 1, and optionally other therapeutic ingredients.

3. The composition of claim 2 in unit dosage form.

4. The composition of claim 3, further comprising one ore more other active ingredients.

5. The use of a compound as described in claim 1 to prepare a medicament for inhibiting HIV.

6. A compound according to claim 1 for use in a method for inhibiting HIV.