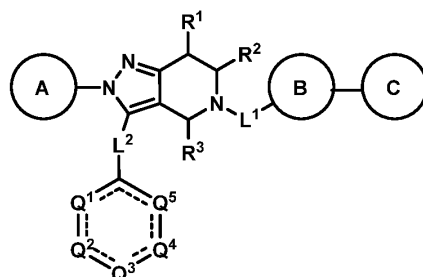


WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (I)

- 5 or a pharmaceutically acceptable salt or solvate thereof, wherein:

Q^1 , Q^2 , Q^3 , Q^4 , and Q^5 are defined according to **(AA)** or **(BB)** below:

(AA)

- 10 Q^1 and Q^5 are independently selected from the group consisting of N, CH, and CR^{QA} ;

Q^2 , Q^3 , and Q^4 are independently selected from the group consisting of N, CH, CR^{QA} , and CR^{QB} , provided that at least one of Q^2 , Q^3 , and Q^4 is CR^{QB} ;

- 15 each $\equiv$ is a single bond or double bond, provided that the ring including Q^1 - Q^5 is aromatic;

(BB)

Q^1 is a bond;

- 20 Q^2 , Q^3 , Q^4 , and Q^5 are independently selected from the group consisting of O, S, N, NH, NR^c , CH, CR^{QA} , and CR^{QB} , provided that at least one of Q^2 , Q^3 , Q^4 , and Q^5 is CR^{QB} ;

each $\equiv$ is a single bond or double bond, provided that the ring including Q^1 - Q^5 is aromatic;

- 25 R^{QB} is $P(=O)R^aR^b$, wherein R^a and R^b are independently selected from the group consisting of C_{1-6} alkyl which is optionally substituted with from 1-6 substituents each

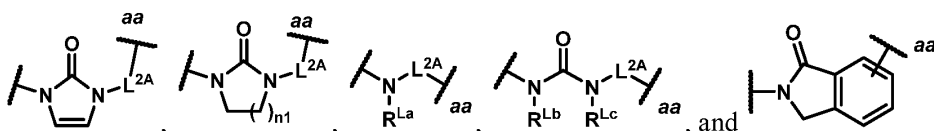
independently selected from the group consisting of C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, and halo; C₃₋₆ cycloalkyl optionally substituted with from 1-3 substituents each independently selected from the group consisting of C₁₋₃ alkyl and halo; and C₆₋₁₀ aryl optionally substituted with from 1-3 independently selected C₁₋₃ alkyl; or

5 R^a and R^b taken together with the phosphorous atom to which each is attached form a ring including from 5-8 ring atoms, wherein from 0-2 ring atoms (in addition to the phosphorous attached to R^a and R^b) are heteroatoms each independently selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with from 1-3 independently selected C₁₋₆ alkyl;

10 each R^{QA} is independently selected from the group consisting of: (a) halo; (b) cyano; (c) OH; (d) -NR^cR^d; (e) C(=O)NR^cR^d; (f) S(=O)₀₋₂R^e; (g) C₁₋₆ alkyl optionally substituted with from 1-6 independently selected R^f; (h) C₁₋₆ alkoxy optionally substituted with from 1-6 substituents each independently selected from the group consisting of: hydroxy, halo, and C₁₋₆ alkoxy; (i) 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C₁₋₆ alkyl and C(=O)(C₁₋₆ alkyl); (j) C₆₋₁₀ aryl optionally substituted with from 1-3 independently selected C(=O)(C₁₋₆ alkyl); and (k) 5-10 membered heteroaryl optionally substituted with from 1-6 independently selected R^g;

20 or a pair of R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached, forms a ring including from 5-8 ring atoms, wherein from 0-2 ring atoms are heteroatoms each independently selected from the group consisting of O, N, and S, wherein said ring is optionally substituted with from 1-2 independently selected R^h groups;

25 L² is selected from the group consisting of:



wherein *aa* represents the point of attachment to the ring containing Q¹-Q⁵;

*n*₁ is an integer from 1-3;

L^{2A} is a bond or C₁₋₁₀ alkylene;

R^{La} is selected from the group consisting of H, C_{1-6} alkyl, and $C(=O)(C_{1-6}$ alkyl);

each of R^{Lb} and R^{Lc} is independently selected from the group consisting of H and C_{1-6} alkyl;

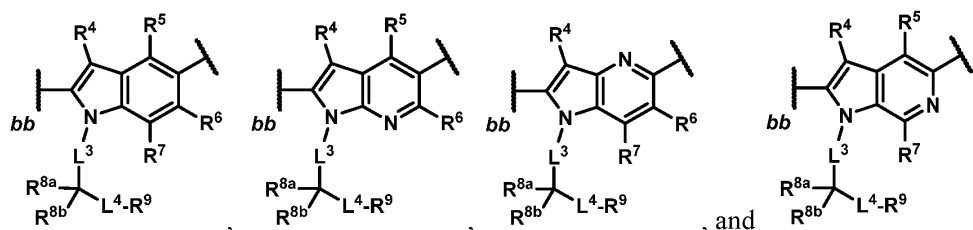
5 Ring A is C_{6-10} aryl, C_{5-7} cycloalkyl, 5-7 membered heterocyclyl, or 5-10 membered heteroaryl, each of which is optionally substituted with from 1-5 substituents each independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^1 , R^2 , and R^3 are each independently selected from the group consisting of H and
10 C_{1-6} alkyl which is optionally substituted with from 1-6 substituents each independently selected from the group consisting of halo, -OH, and C_{1-6} alkoxy;

L^1 is selected from the group consisting of: $-C(=O)-$, $-CH_2-$, $-CH(C_{1-6}$ alkyl)-, and $-S(=O)_2-$;

15

Ring B is selected from the group consisting of:



wherein *bb* represents point of attachment to L^1 ;

R^4 , R^5 , R^6 , and R^7 are independently selected from the group consisting of: H,
20 halo, and C_{1-6} alkyl;

L^3 is a bond or C_{1-3} alkylene;

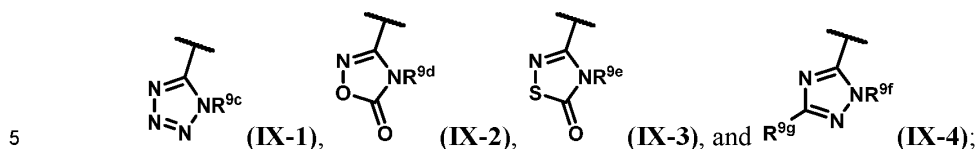
L^4 is a bond or C_{1-5} alkylene;

R^{8a} and R^{8b} are independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from
25 the group consisting of: halo and C_{3-15} cycloalkyl; or

R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-15} cycloalkyl ring which is optionally substituted with from 1-3 independently selected

C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with from 1-6 independently selected R^f,

R⁹ is selected from the group consisting of: C(=O)OH, C(=O)(OC₁₋₆ alkyl), C(=O)NR^{9a}R^{9b}, (IX-1), (IX-2), (IX-3), and (IX-4):



R^{9a} is H or C₁₋₆ alkyl;

R^{9b} is H, C₁₋₆ alkyl, C(=O)(C₁₋₆ alkyl), S(O)₀₋₂(C₁₋₆ alkyl), or cyano;

R^{9c}, R^{9d}, R^{9e}, R^{9f}, and R^{9g} are each independently selected from the group consisting of: H; C₁₋₆ alkyl optionally substituted with from 1-6 independently selected
10 halo and C₁₋₆ alkoxy; and C(=O)(C₁₋₆ alkyl);

Ring C is selected from the group consisting of 3-12 membered heterocyclyl; C₃₋₁₅ cycloalkyl; and 5-10 membered heteroaryl, each of which is optionally substituted with from 1-3 R^{Ca},

15 each R^{Ca} is independently selected from the group consisting of: halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and NR^cR^d;

or a pair of R^{Ca} on the same or different ring atoms, taken together with the ring atom(s) to which each is attached, forms a carbocyclic ring including from 3-8 ring atoms;

20 each R^c and R^d are independently selected from the group consisting of: H, C₁₋₆ alkyl, C(=O)(C₁₋₆ alkyl), C(=O)(C₃₋₆ cycloalkyl), C(=O)O(C₁₋₆ alkyl), S(O)₁₋₂(C₁₋₆ alkyl), and S(O)₁₋₂(C₃₋₆ cycloalkyl), wherein the C₁₋₆ alkyl, C(=O)(C₁₋₆ alkyl), C(=O)(C₃₋₆ cycloalkyl), C(=O)O(C₁₋₆ alkyl), S(O)₁₋₂(C₁₋₆ alkyl), and S(O)₁₋₂(C₃₋₆ cycloalkyl) are each optionally substituted with from 1-6 substituents independently selected from the group
25 consisting of: -OH, halo, and C₁₋₆ alkoxy;

R^c is H, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

each R^f is independently selected from the group consisting of halo, -OH, NR^cR^d, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, and 3-12 membered heterocyclyl which is optionally

substituted with from 1-4 substituents each independently selected from the group consisting of -OH, C₁₋₆ alkyl, and 3-12 membered heterocyclyl;

each R^g is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ alkoxy, NR^cR^d, and 3 to 12 membered heterocyclyl optionally substituted with one or
5 more substituents each independently selected from the group consisting of C₁₋₆ alkyl and C(=O)C₁₋₆ alkyl; and

each R^h is independently selected from the group consisting of halo, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -OH, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C₁₋₃ alkoxy, and C₁₋₃ haloalkoxy.

10

2. The compound of claim 1, wherein Q¹, Q², Q³, Q⁴, and Q⁵ are as defined according to (AA).

3. The compound of claim 2, wherein Q³ is CR^{QB}.

15

4. The compound of claim 3, wherein Q⁴ is N, CH, or CR^{QA}.

5. The compound of claim 2, wherein Q⁴ is CR^{QB}; and Q³ is N, CH, or CR^{QA}.

20

6. The compound of any one of claims 2-5, wherein Q¹ is CH.

7. The compound of any one of claims 2-6, wherein Q² is CH.

8. The compound of any one of claims 2-7, wherein Q⁵ is CR^{QA}.

25

9. The compound of any one of claims 2-7, wherein Q⁵ is CH.

10. The compound of claim 2, wherein Q³ is CR^{QB}; and each one of Q¹, Q², Q⁴, and Q⁵ is independently CH or CR^{QA}.

30

11. The compound of claim 10, wherein each one of Q¹, Q², Q⁴, and Q⁵ is CH.

12. The compound of claim 10, wherein one of Q^1 , Q^2 , Q^4 , and Q^5 is CR^{QA} ; and each remaining one of Q^1 , Q^2 , Q^4 , and Q^5 is CH.

5 13. The compound of claim 12, wherein Q^4 is CR^{QA} ; and Q^1 , Q^2 , and Q^5 are CH.

14. The compound of claim 10, two of Q^1 , Q^2 , Q^4 , and Q^5 are independently selected CR^{QA} ; and each remaining one of Q^1 , Q^2 , Q^4 , and Q^5 is CH.

10

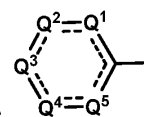
15. The compound of claim 2, wherein Q^3 is CR^{QB} ; one of Q^1 , Q^2 , Q^4 , and Q^5 is N; and each remaining one of Q^1 , Q^2 , Q^4 , and Q^5 is independently CH or CR^{QA} .

16. The compound of claim 15, wherein Q^4 is N.

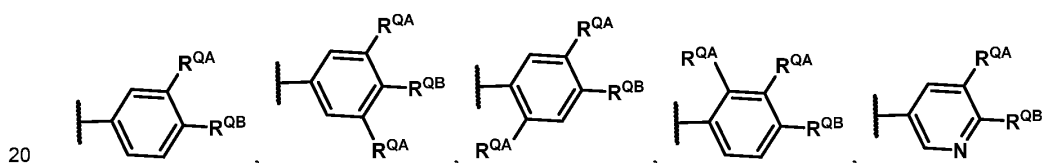
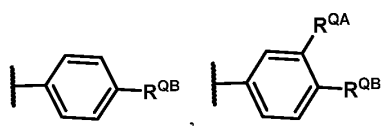
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17. The compound of claims 15 or 16, wherein Q^1 , Q^2 , and Q^5 are CH.

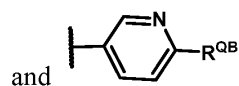
18. The compound of claim 2, wherein Q^3 is CR^{QB} ; and the



moiety is selected from the group consisting of:



20



19. The compound of claim 2, wherein Q^4 is CR^{QB} ; and each one of Q^1 , Q^2 , Q^3 , and Q^5 is independently CH or CR^{QA} .

20. The compound of claim 19, wherein each one of Q^1 , Q^2 , Q^3 , and Q^5 is CH.

5

21. The compound of claim 19, wherein one of Q^1 , Q^2 , Q^3 , and Q^5 is CR^{QA} , and each remaining one of Q^1 , Q^2 , Q^3 , and Q^5 is CH.

22. The compound of claim 21, wherein Q^5 is CR^{QA} , and Q^1 , Q^2 , and Q^3 are
10 CH.

23. The compound of claim 19, wherein two of Q^1 , Q^2 , Q^3 , and Q^5 are independently selected CR^{QA} ; and each remaining one of Q^1 , Q^2 , Q^3 , and Q^5 is CH.

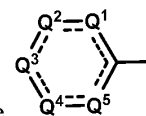
24. The compound of claim 23, wherein Q^2 and Q^3 are independently selected CR^{QA} ; and Q^1 and Q^5 are CH.

15

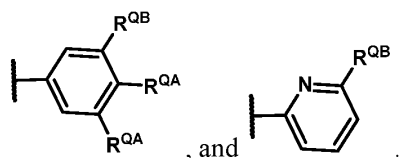
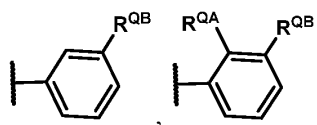
25. The compound of claim 2, wherein Q^4 is CR^{QB} ; one of Q^1 , Q^2 , Q^3 , and Q^5 is N; and each remaining one of Q^1 , Q^2 , Q^3 , and Q^5 is independently CH or CR^{QA} .

20

26. The compound of claim 2, wherein Q^4 is CR^{QB} , and the



moiety is selected from the group consisting of:



27. The compound of any one of claims 1-26, wherein R^{QB} is $P(=O)R^aR^b$, wherein R^a and R^b are independently selected from the group consisting of C_{1-6} alkyl and C_{3-6} cycloalkyl.

5

28. The compound of any one of claims 1-27, wherein R^{QB} is $P(=O)R^aR^b$, wherein R^a and R^b are independently C_{1-3} alkyl.

29. The compound of claim 28, wherein R^a and R^b are the same.

10

30. The compound of any one of claims 1-29, wherein R^{QB} is $P(=O)Me_2$.

31. The compound of any one of claims 1-29, wherein R^{QB} is $P(=O)Et_2$.

15

32. The compound of any one of claims 1-29, wherein R^{QB} is $P(=O)iPr_2$.

33. The compound of claim 28, wherein R^a and R^b are different.

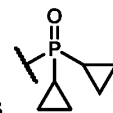
34. The compound of any one of claims 1-27 or 33, wherein R^{QB} is $P(=O)(Me)(tBu)$.

20

35. The compound of any one of claims 1-27, wherein R^{QB} is $P(=O)R^aR^b$, wherein R^a and R^b are each independently C_{3-6} cycloalkyl.

25

36. The compound of any one of claims 1-27 or 35, wherein R^{QB} is



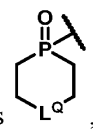
37. The compound of any one of claims 1-26, wherein R^{QB} is $P(=O)R^aR^b$, wherein R^a and R^b taken together with the phosphorous atom to which each is attached

forms a ring including from 5-8 ring atoms, wherein from 0-2 ring atoms (in addition to the phosphorous attached to R^a and R^b) are heteroatoms each independently selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with from 1-3 independently selected C₁₋₆ alkyl.

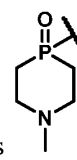
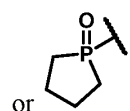
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38. The compound of any one of claims 1-26 or 37, wherein R^{QB} is P(=O)R^aR^b, wherein R^a and R^b taken together with the phosphorous atom to which each is attached forms a ring including from 5-6 ring atoms, wherein from 0-1 ring atom (in addition to the phosphorous attached to R^a and R^b) is a heteroatom selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with from 1-2 independently selected C₁₋₆ alkyl.

10

39. The compound of any one of claims 1-26 or 37-38, wherein R^{QB} is , wherein L^Q is a bond, CH₂, O, S, NH, or N(C₁₋₆ alkyl).

15

40. The compound of any one of claims 1-26 or 37-39, wherein R^{QB} is ,
or .

41. The compound of any one of claims 1-40, wherein one occurrence of R^{QA} is halo.

20

42. The compound of claim 41, wherein one occurrence of R^{QA} is -F.

43. The compound of any one of claims 1-40, wherein one occurrence of R^{QA} is $-OH$.
44. The compound of any one of claims 1-40, wherein one occurrence of R^{QA} is NR^cR^d .
45. The compound of claim 44, wherein one occurrence of R^{QA} is $NH(C_{1-3} \text{ alkyl})$.
46. The compound of claim 44, wherein one occurrence of R^{QA} is NH_2 .
47. The compound of claim 44, wherein one occurrence of R^{QA} is $N(C_{1-3} \text{ alkyl})_2$.
48. The compound of claim 44, wherein one occurrence of R^{QA} is selected from the group consisting of $NHC(=O)(C_{1-6} \text{ alkyl})$, $NHC(=O)(C_{3-6} \text{ cycloalkyl})$, $NHC(=O)O(C_{1-6} \text{ alkyl})$, $NHS(O)_{1-2}(C_{1-6} \text{ alkyl})$, and $NHS(O)_{1-2}(C_{3-6} \text{ cycloalkyl})$.
49. The compound of claim 48, wherein one occurrence of R^{QA} is $NHC(=O)(C_{1-3} \text{ alkyl})$, $NHC(=O)(C_{3-6} \text{ cycloalkyl})$, or $NHS(O)_2(C_{1-3} \text{ alkyl})$.
50. The compound of any one of claims 1-40, wherein one occurrence of R^{QA} is 5-6 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of $C_{1-6} \text{ alkyl}$ and $C(=O)(C_{1-6} \text{ alkyl})$.
51. The compound of claim 50, wherein one occurrence of R^{QA} is morpholinyl.
52. The compound of any one of claims 1-40, wherein one occurrence of R^{QA} is $C_{1-6} \text{ alkoxy}$ optionally substituted with from 1-6 substituents each independently selected from the group consisting of: hydroxy, halo, and $C_{1-6} \text{ alkoxy}$.

53. The compound of any one of claims 1-40 or 52, wherein one occurrence of R^{QA} is C_{1-6} alkoxy optionally substituted with from 1-6 independently selected halo.

5 **54.** The compound of claim 53, wherein R^{QA} is $-OMe$, $-OCF_3$, or $-OCHF_2$.

55. The compound of any one of claims 1-40, wherein one occurrence of R^{QA} is C_{1-6} alkyl optionally substituted with from 1-6 independently selected R^f .

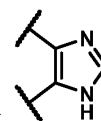
10 **56.** The compound of any one of claims 1-40 or 55, wherein one occurrence R^{QA} is C_{1-3} alkyl or C_{1-3} alkyl substituted with from 1-6 independently selected halo, optionally wherein R^{QA} is methyl, $-CF_3$, or $-CHF_2$.

57. The compound of any one of claims 41-56, wherein each remaining R^{QA}
15 when present is an independently selected halo.

58. The compound of any one of claims 1-40, wherein a pair of R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached, forms a ring including from 5-6 ring atoms, wherein from 1-2 ring atoms are heteroatoms each
20 independently selected from the group consisting of O, N, and S, wherein said ring is optionally substituted with from 1-2 independently selected R^h groups.

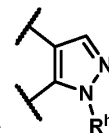
59. The compound of claim 58, wherein a pair of R^{QA} on adjacent carbon

atoms, taken together with the atom to which each is attached forms:

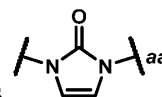


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60. The compound of claim 58, wherein a pair of R^{QA} on adjacent carbon



atoms, taken together with the atom to which each is attached forms:



61. The compound of any one of claims 1-60, wherein L^2 is

5

62. The compound of any one of claims 1-61, wherein Ring A is C_{6-10} aryl or 5-10 membered heteroaryl, each of which is optionally substituted with from 1-4 substituents each independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy.

10

63. The compound of any one of claims 1-62, wherein Ring A is phenyl or pyridyl, each of which is optionally substituted with from 2-4 substituents each independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy.

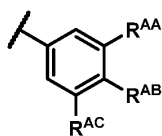
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64. The compound of claim 63, wherein Ring A is phenyl, which is optionally substituted with from 2-4 substituents each independently selected from the group consisting of halo and C_{1-6} alkyl.

20

65. The compound of claim 63, wherein Ring A is pyridyl, which is optionally substituted with from 2-4 substituents each independently selected from the group consisting of halo and C_{1-6} alkyl.

66. The compound of any one of claims 1-64, wherein Ring A is



25

, wherein R^{AA} , R^{AB} , and R^{AC} are independently halo or C_{1-6} alkyl.

67. The compound of any one of claims 1-66, wherein R^1 , R^2 , and R^3 are H.

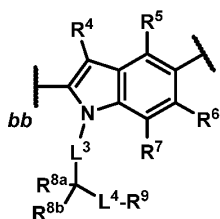
68. The compound of any one of claims 1-66, wherein R^1 and R^2 are H; and
 5 R^3 is C_{1-6} alkyl.

69. The compound of claim 68, wherein R^3 is methyl.

70. The compound of any one of claims 1-66, wherein R^1 is H; and R^2 and R^3
 10 are independently selected C_{1-6} alkyl.

71. The compound of any one of claims 1-70, wherein L^1 is $C(=O)$.

15 72. The compound of any one of claims 1-71, wherein Ring B is



73. The compound of any one of claims 1-72, wherein R^4 , R^5 , and R^6 are each
 H or halo.

20

74. The compound of any one of claims 1-73, wherein R^4 , R^5 , and R^6 are each
 H or -F.

75. The compound of any one of claims 1-74, wherein R^4 , R^5 , and R^6 are each
 25 H.

76. The compound of any one of claims 1-74, wherein R^4 and R^5 are H; and R^6 is -F.

77. The compound of any one of claims 1-76, wherein R^7 is H.

5

78. The compound of any one of claims 1-76, wherein R^7 is -F.

79. The compound of any one of claims 1-78, wherein at least one of L^3 and L^4 is a bond.

10

80. The compound of any one of claims 1-79, wherein both of L^3 and L^4 are bonds.

81. The compound of any one of claims 1-79, wherein L^3 is a bond; and L^4 is C_{1-2} alkylene.

15

82. The compound of any one of claims 1-79, wherein L^4 is a bond; and L^3 is C_{1-2} alkylene.

83. The compound of any one of claims 1-78, wherein L^3 and L^4 are each independently C_{1-2} alkylene.

20

84. The compound of any one of claims 1-83, wherein R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-8} cycloalkyl ring which is optionally substituted with from 1-2 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with from 1-3 independently selected R^f .

25

85. The compound of any one of claims 1-84, wherein R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-5} cycloalkyl ring which is optionally substituted with from 1-2 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with from 1-3 independently selected R^f .

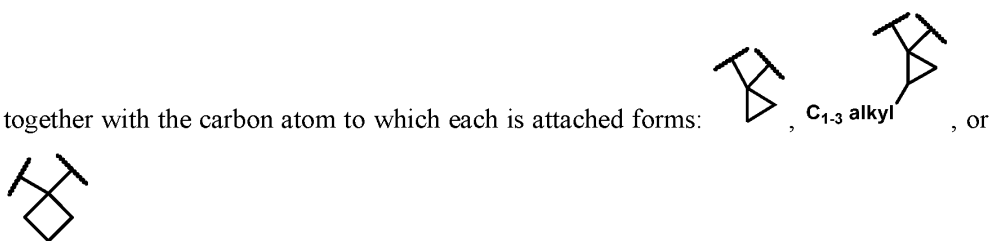
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86. The compound of any one of claims 1-85, wherein R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-4} cycloalkyl ring which is optionally substituted with from 1-2 independently selected C_{1-6} alkyl.

5

87. The compound of any one of claims 1-83, wherein R^{8a} and R^{8b} taken

together with the carbon atom to which each is attached forms:



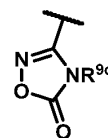
10

88. The compound of any one of claims 1-83 or 87, wherein R^{8a} and R^{8b} taken

together with the carbon atom to which each is attached forms:



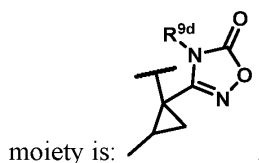
89. The compound of any one of claims 1-88, wherein R^9 is



(IX-2).

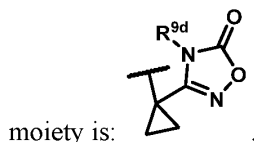
15

90. The compound of any one of claims 1-79, wherein the $L^3-C(R^{8a}R^{8b})-L^4-R^9$



moiety is:

91. The compound of any one of claims 1-79, wherein the $L^3-C(R^{8a}R^{8b})-L^4-R^9$



92. The compound of any one of claims 89-91, wherein R^{9d} is H or C_{1-6} alkyl.

93. The compound of any one of claims 89-92, wherein R^{9d} is H.

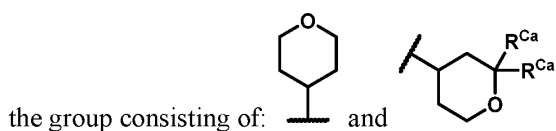
94. The compound of any one of claims 1-93, wherein Ring C is 3-12 membered heterocyclyl which is optionally substituted with from 1-3 independently selected R^{Ca} .

95. The compound of any one of claims 1-94, wherein Ring C is 4-8 membered heterocyclyl which is optionally substituted with from 1-3 independently selected R^{Ca} .

96. The compound of any one of claims 1-95, wherein Ring C is 5-6 membered heterocyclyl which is optionally substituted with from 1-3 independently selected R^{Ca} .

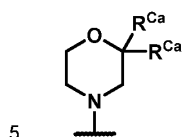
97. The compound of any one of claims 1-96, wherein Ring C is tetrahydropyranyl which is optionally substituted with from 1-3 independently R^{Ca} .

98. The compound of any one of claims 1-97, wherein Ring C is selected from



99. The compound of any one of claims 1-96, wherein Ring C is morpholinyl which is optionally substituted with from 1-3 independently selected R^{Ca} .

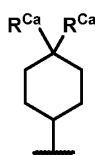
100. The compound of any one of claims 1-96 or 99, wherein Ring C is



101. The compound of any one of claims 1-93, wherein Ring C is C_{3-10} cycloalkyl which is optionally substituted with from 1-3 R^{Ca} .

102. The compound of any one of claims 1-93 or 101, wherein Ring C is C_{3-8} cycloalkyl which is optionally substituted with from 1-3 R^{Ca} .

103. The compound of any one of claims 1-93 or 101-102, wherein Ring C is



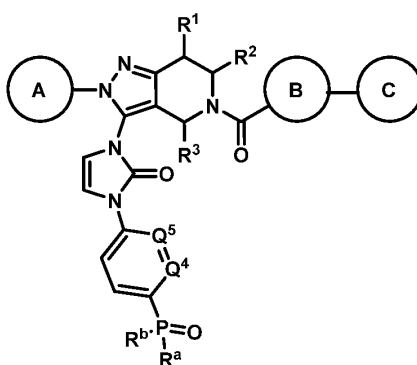
104. The compound of any one of claims 1-103, wherein each R^{Ca} is independently selected from the group consisting of: halo and C_{1-6} alkyl.

105. The compound of any one of claims 1-104, wherein each R^{Ca} is independently C_{1-6} alkyl.

106. The compound of any one of claims 1-103, wherein a pair of R^{Ca} on the same or different ring atoms, taken together with the ring atom(s) to which each is attached, forms a carbocyclic ring including from 3-6 ring atoms.

107. The compound of any one of claims 1-103 or 106, wherein a pair of R^{Ca} on the same ring atom, taken together with the ring atom to which each is attached, forms a carbocyclic ring including from 3-5 ring atoms.

5 **108.** The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (IA):



Formula (IA)

wherein Q^4 and Q^5 are independently selected from the group consisting of: N,
 10 CH, and CR^{QA} ,
 or a pharmaceutically acceptable salt or solvate thereof.

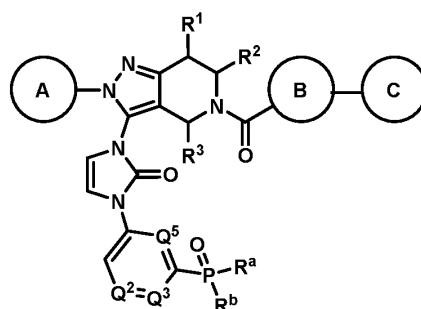
109. The compound of claim 108, wherein each of Q^4 and Q^5 is CH.

15 **110.** The compound of claim 108, wherein Q^4 is CR^{QA} , and Q^5 is CH.

111. The compound of claim 108, wherein Q^4 is N; and Q^5 is CR^{QA} or CH, optionally wherein Q^5 is CH.

20 **112.** The compound of claim 108, wherein Q^4 is CR^{QA} , and Q^5 is CR^{QA} .

113. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (IB):



Formula (IB)

wherein Q^2 , Q^3 , and Q^5 are independently selected from the group consisting of:
N, CH, and CR^{QA} ;

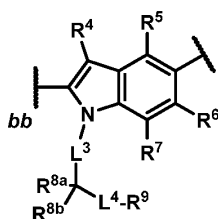
5 or a pharmaceutically acceptable salt or solvate thereof.

114. The compound of claim 113, wherein each of Q^2 , Q^3 , and Q^5 is CH.

115. The compound of claim 113, wherein Q^5 is CR^{QA} ; and each of Q^2 and Q^3
10 is CH.

116. The compound of claim 113, wherein Q^5 is CH; and Q^2 and Q^3 are
independently selected CR^{QA} .

15 117. The compound of any one of claims 108-116, wherein Ring B is



118. The compound of any one of claims 108-117, wherein at least one of L^3
and L^4 is a bond.

20

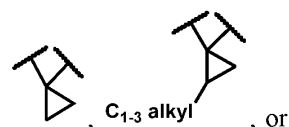
119. The compound of any one of claims 108-118, wherein both of L^3 and L^4 are bonds.

120. The compound of any one of claims 108-119, wherein R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-5} cycloalkyl ring which is optionally substituted with from 1-2 independently selected C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with from 1-3 independently selected R^f .

121. The compound of claim 120, wherein R^{8a} and R^{8b} taken together with the carbon atom to which each is attached forms a C_{3-4} cycloalkyl ring which is optionally substituted with from 1-2 independently selected C_{1-6} alkyl.

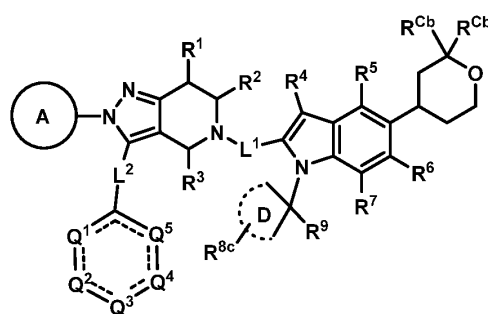
122. The compound of any one of claims 108-121, wherein R^{8a} and R^{8b} taken

together with the carbon atom to which each is attached forms:



15

123. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (IC):



Formula (IC)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Ring D is a C_{3-6} cycloalkyl;

R^{8c} is selected from the group consisting of H and C_{1-6} alkyl optionally substituted with from 1-3 independently selected R^f ; and

each R^{Cb} is independently selected from the group consisting of H and R^{Ca} .

5 **124.** The compound of claim 123, wherein Ring D is cyclopropyl.

125. The compound of claim 123, wherein Ring D is cyclobutyl.

126. The compound of any one of claims 123-125, wherein R^{8c} is H.

10

127. The compound of any one of claims 123-125, wherein R^{8c} is C_{1-3} alkyl.

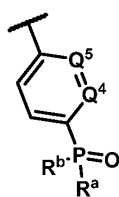
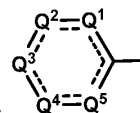
128. The compound of claim 127, wherein R^{8c} is methyl.

15

129. The compound of any one of claims 123-128, wherein each R^{Cb} is H.

130. The compound of any one of claims 123-128, wherein each R^{Cb} is independently C_{1-6} alkyl.

131. The compound of any one of claims 123-130, wherein the



20 moiety is $R^b-P(=O)(R^a)-$ wherein Q^4 and Q^5 are independently selected from the group consisting of N, CH, and CR^{QA} .

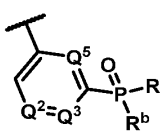
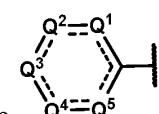
132. The compound of claim 131, wherein each of Q^4 and Q^5 is CH.

25

133. The compound of claim 131, wherein Q^4 is CR^{QA} , and Q^5 is CH.

134. The compound of claim 131, wherein Q^4 is N; and Q^5 is CR^{QA} or CH, optionally wherein Q^5 is CH.

5 **135.** The compound of claim 131, wherein Q^4 is CR^{QA} , and Q^5 is CR^{QA} .

136. The compound of any one of claims 123-130, wherein the moiety is  , wherein Q^2 , Q^3 , and Q^5 are independently selected from the group consisting of N, CH, and CR^{QA} .

10

137. The compound of claim 136, wherein each of Q^2 , Q^3 , and Q^5 is CH.

138. The compound of claim 136, wherein Q^5 is CR^{QA} , and each of Q^2 and Q^3 is CH.

15

139. The compound of claim 136, wherein Q^5 is CH; and Q^2 and Q^3 are independently selected CR^{QA} .

140. The compound of any one of claims 108-138, wherein R^a and R^b are each independently selected from the group consisting of C_{1-6} alkyl and C_{3-6} cycloalkyl.

141. The compound of any one of claims 108-140, wherein R^a and R^b are each independently C_{1-3} alkyl.

25 **142.** The compound of any one of claims 108-141, wherein R^a and R^b are each methyl.

143. The compound of any one of claims 108-141, wherein R^a and R^b are each ethyl.

5 **144.** The compound of any one of claims 108-141, wherein R^a and R^b are each isopropyl.

145. The compound of any one of claims 108-140, wherein R^a is methyl; and R^b is tert-butyl.
10

146. The compound of any one of claims 108-140, wherein R^a and R^b are independently selected C₃₋₆ cycloalkyl.

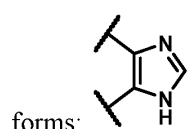
147. The compound of any one of claims 108-140 or 146, wherein R^a and R^b are both cyclopropyl.
15

148. The compound of any one of claims 108-147, wherein each R^{QA} is selected from the group consisting of: halo; cyano; OH; NR^cR^d; C₁₋₆ alkyl optionally substituted with from 1-6 independently selected R^f; C₁₋₆ alkoxy optionally substituted with from 1-6 substituents each independently selected from the group consisting of: hydroxy, halo, and C₁₋₆ alkoxy; and 3-12 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of C₁₋₆ alkyl and C(=O)(C₁₋₆ alkyl).
20

25 **149.** The compound of any one of claims 108-148, wherein each R^{QA} is selected from the group consisting of: -F, OH, NH₂, NHMe, NHEt, NHiPr, N(Me)₂, NHC(=O)(cyclopropyl), NHS(O)₂Me, methyl, CF₃, CHF₂, OMe, OCF₃, OCHF₂, and morpholinyl.

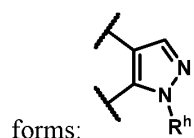
150. The compound of any one of claims 108-147, wherein a pair of R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached, forms a ring including from 5-6 ring atoms, wherein from 1-2 ring atoms are heteroatoms each independently selected from the group consisting of O, N, and S, wherein said ring is
 5 optionally substituted with from 1-2 independently selected R^h groups.

151. The compound of any one of claims 108-147 or 150, wherein a pair of R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached

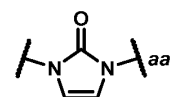


10

152. The compound of any one of claims 108-147 or 150, wherein a pair of R^{QA} on adjacent carbon atoms, taken together with the atom to which each is attached



153. The compound of any one of claims 123-152, wherein L^2 is



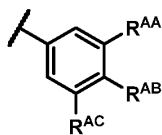
15

154. The compound of any one of claims 108-153, wherein Ring A is phenyl or pyridyl, each of which is optionally substituted with from 2-4 substituents each independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and
 20 C_{1-6} alkoxy.

155. The compound of any one of claims 108-154, wherein Ring A is phenyl, which is optionally substituted with from 2-4 substituents each independently selected from the group consisting of halo and C_{1-6} alkyl.

25

156. The compound of any one of claims 108-155, wherein Ring A is



, wherein R^{AA} , R^{AB} , and R^{AC} are independently halo or C_{1-6} alkyl.

157. The compound of any one of any one of claims 108-156, wherein R^1 and
5 R^2 are H.

158. The compound of any one of claims 108-157, wherein R^3 is H.

159. The compound of any one of claims 108-157, wherein R^3 is C_{1-6} alkyl.
10

160. The compound of any one of claims 108-156, wherein R^1 and R^2 are H;
and R^3 is C_{1-6} alkyl.

161. The compound of claims 159 or 160, wherein R^3 is methyl.
15

162. The compound of any one of claims 108-161, wherein L^1 is $C(=O)$.

163. The compound of any one of claims 108-162, wherein R^4 , R^5 , and R^6 are
each H or halo.
20

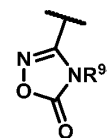
164. The compound of any one of claims 108-163, wherein R^4 , R^5 , and R^6 are
each H or -F.

165. The compound of any one of claims 108-164, wherein R^4 , R^5 , and R^6 are
25 each H.

166. The compound of any one of claims 108-164, wherein R^4 and R^5 are H;
and R^6 is -F.

167. The compound of any one of claims 108-166, wherein R^7 is H.

168. The compound of any one of claims 108-166, wherein R^7 is -F.



5 169. The compound of any one of claims 108-168, wherein R^9 is (IX-2).

170. The compound of claim 169, wherein R^{9d} is H.

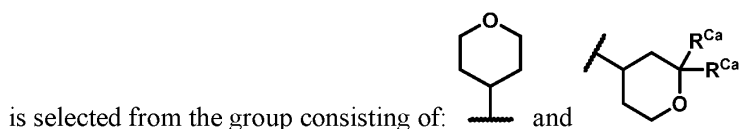
10 171. The compound of any one of claims 108-122 or 140-170, wherein Ring C is 3-12 membered heterocyclyl which is optionally substituted with from 1-3 independently selected R^{Ca} .

15 172. The compound of any one of claims 108-122 or 140-171, wherein Ring C is 5-6 membered heterocyclyl which is optionally substituted with from 1-3 independently selected R^{Ca} .

173. The compound of any one of claims 108-122 or 140-172, wherein Ring C is tetrahydropyranyl which is optionally substituted with from 1-3 independently R^{Ca} .

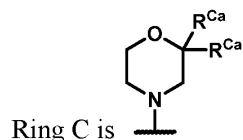
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174. The compound of any one of claims 108-122 or 140-173, wherein Ring C



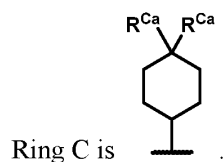
25 175. The compound of any one of claims 108-122 or 140-172, wherein Ring C is morpholinyl which is optionally substituted with from 1-3 independently selected R^{Ca} .

176. The compound of any one of claims 108-122, 140-172, or 175, wherein



177. The compound of any one of claims 108-122 or 140-170, wherein Ring C
5 is C₃₋₈ cycloalkyl which is optionally substituted with from 1-3 R^{Ca}.

178. The compound of any one of claims 108-122, 140-170, or 177, wherein



10 179. The compound of any one of claims 108-122 or 140-178, wherein each
R^{Ca} is independently C₁₋₆ alkyl.

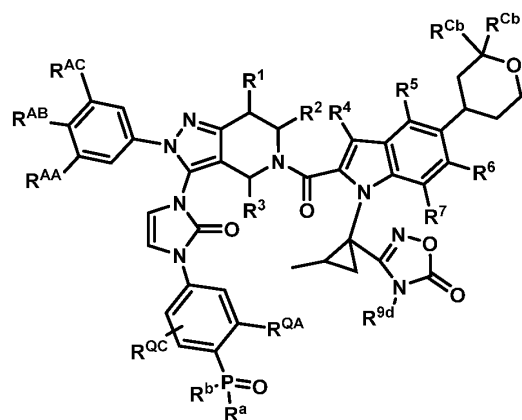
180. The compound of any one of claims 108-122 or 140-178, wherein each
R^{Ca} is -F.

15

181. The compound of any one of claims 108-122 or 140-178, wherein a pair of
R^{Ca} on the same or different ring atoms, taken together with the ring atom(s) to which
each is attached, forms a carbocyclic ring including from 3-6 ring atoms.

20 182. The compound of any one of claims 108-122 or 140-178, wherein a pair of
R^{Ca} on the same ring atom, taken together with the ring atom to which each is attached,
forms a carbocyclic ring including from 3-5 ring atoms.

25 183. The compound of claim 1, wherein the compound of Formula (I) is a
compound of Formula (II):



Formula (ID)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{AA} , R^{AB} , and R^{AC} are independently halo or C_{1-6} alkyl;

5 R^{QC} is H or halo; and

each R^{Cb} is independently selected from the group consisting of H and R^{Ca} .

184. The compound of claim 183, wherein R^1 and R^2 are H.

10 **185.** The compound of claims 183 or 184, wherein R^3 is C_{1-3} alkyl.

186. The compound of any one of claims 183-185, wherein R^3 is methyl.

15 **187.** The compound of any one of claims 183-186, wherein R^4 , R^5 , R^6 , and R^7 are H.

188. The compound of any one of claims 183-187, wherein R^{9d} is H.

20 **189.** The compound of any one of claims 183-188, wherein R^{AA} and R^{AC} are independently C_{1-6} alkyl.

190. The compound of any one of claims 183-189, wherein R^{AA} and R^{AC} are methyl.

191. The compound of any one of claims 183-190, wherein R^{AB} is halo.

5

192. The compound of any one of claims 183-191, wherein R^{AB} is -F.

193. The compound of any one of claims 183-192, wherein each R^{Cb} is H or methyl, optionally wherein each R^{Cb} is H.

10

194. The compound of any one of claims 183-193, wherein R^a and R^b are independently C_{1-3} alkyl.

195. The compound of any one of claims 183-194, wherein R^a and R^b are methyl.

15

196. The compound of any one of claims 183-194, wherein R^a and R^b are ethyl.

197. The compound of any one of claims 183-194, wherein R^a and R^b are isopropyl.

20

198. The compound of any one of claims 183-193, wherein R^a is methyl; and R^b is tert-butyl.

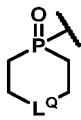
199. The compound of any one of claims 183-193, wherein R^a and R^b are independently C_{3-6} cycloalkyl.

25

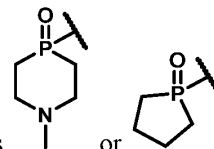
200. The compound of any one of claims 183-193 or 199, wherein R^a and R^b are each cyclopropyl.

30

201. The compound of any one of claims 183-193, wherein $P(=O)R^aR^b$ is



, wherein L^Q is a bond, CH_2 , O, S, NH, or $N(C_{1-6} \text{ alkyl})$.



202. The compound of 201, wherein $P(=O)R^aR^b$ is

or

5

203. The compound of any one of claims 183-202, wherein R^{QA} is $-F$.

204. The compound of any one of claims 183-202, wherein R^{QA} is $-OH$.

10

205. The compound of any one of claims 183-202, wherein R^{QA} is NR^cR^d .

206. The compound of any one of claims 183-202 or 205, wherein R^{QA} is $NH(C_{1-3} \text{ alkyl})$.

15

207. The compound of any one of claims 183-202 or 205, wherein R^{QA} is NH_2 .

208. The compound of any one of claims 183-202 or 205, wherein R^{QA} is $N(C_{1-3} \text{ alkyl})_2$.

20

209. The compound of any one of claims 183-202 or 205, wherein R^{QA} is $NHC(=O)(C_{1-3} \text{ alkyl})$, $NHC(=O)(C_{3-6} \text{ cycloalkyl})$, or $NHS(O)_2(C_{1-3} \text{ alkyl})$.

210. The compound of any one of claims 183-202, wherein R^{QA} is 5-6 membered heterocyclyl optionally substituted with one or more substituents each independently selected from the group consisting of $C_{1-6} \text{ alkyl}$ and $C(=O)(C_{1-6} \text{ alkyl})$.

25

211. The compound of any one of claims 183-202, wherein R^{QA} is C₁₋₆ alkoxy optionally substituted with from 1-6 independently selected halo.

212. The compound of any one of claims 183-202 or 211, wherein R^{QA} is –
5 OMe, –OCF₃, or –CHF₂.

213. The compound of any one of claims 183-202, wherein R^{QA} is C₁₋₃ alkyl optionally substituted with from 1-6 independently selected halo.

10 214. The compound of any one of claims 183-202 or 213, wherein R^{QA} is methyl, –CF₃, or CHF₂.

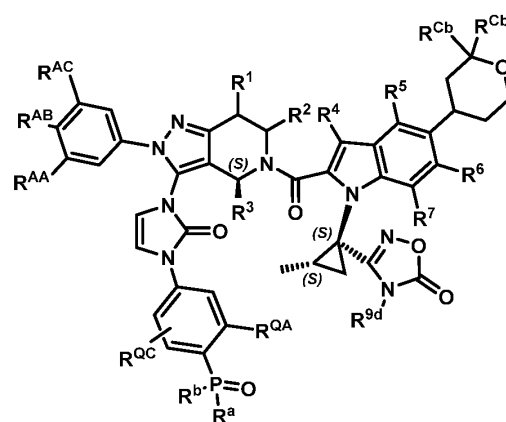
215. The compound of any one of claims 183-214, wherein R^{QC} is H.

15 216. The compound of any one of claims 183-214, wherein R^{QC} is –F.

217. The compound of claim 216, wherein R^{QC} is *meta* to P(=O)R^aR^b.

218. The compound of claims 216 or 217, wherein R^{QC} is *ortho* to R^{QA}.

20 219. The compound of any one of claims 183-218, wherein the compound is a compound of Formula (S, S, S)-(ID)

Formula (*S, S, S*)-(ID)

or a pharmaceutically acceptable salt thereof, wherein R³ is C₁₋₃ alkyl.

5 **220.** The compound of any one of claims 1-219, wherein the compound of Formula I is selected from the group consisting of the compounds in **Table C1** and **Table C2**, or a pharmaceutically acceptable salt or solvate thereof.

10 **221.** A pharmaceutical composition comprising a compound of any one of claims 1-220, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

15 **222.** A method of treating type 2 diabetes mellitus in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-220, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 221.

20 **223.** A method for treating type 2 diabetes mellitus in a patient, the method comprising administering to a patient identified or diagnosed as having type 2 diabetes mellitus a therapeutically effective amount of a compound of any one of claims 1-220, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 221.

224. A method of treating diabetes mellitus in a patient, the method comprising:
a) determining that the patient has type 2 diabetes mellitus; and
b) administering to the patient a therapeutically effective amount of a
5 compound of any one of claims 1–220, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 221.

225. The method of any one of claims 222–224, wherein the step of
determining that the patient has type 2 diabetes mellitus includes performing an assay to
10 determine the level of an analyte in a sample from the patient, wherein the analyte is selected from the group consisting of hemoglobin A1c (HbA1c), fasting plasma glucose, non-fasting plasma glucose, or any combination thereof.

226. The method of claim 225, wherein the level of HbA1c is greater than or
15 about 6.5%.

227. The method of any one of claims 225–226, wherein the level of fasting
plasma glucose is greater than or about 126 mg/dL.

228. The method of any one of claims 225–227, wherein the level of non-
20 fasting plasma glucose is greater than or about 200 mg/dL.

229. The method of any one of claims 222–228, further comprising obtaining a
sample from the patient.

25 230. The method of claim 229, wherein the sample is a body fluid sample.

231. The method of any one of claims 222–230, wherein the patient is about 40
to about 70 years old and is overweight or obese.

30 232. The method of any one of claims 222–231, wherein the patient has a body mass index (BMI) greater than or about 22 kg/m².

233. The method of any one of claims 222-232, wherein the patient has a BMI greater than or about 30 kg/m².

234. The method of any one of claims 222-233, wherein the treatment of type 2 diabetes mellitus comprises a reduction in fasting plasma glucose levels.

235. The method of claim 234, wherein the fasting plasma glucose levels are reduced to about or below 100 mg/dL.

236. The method of any one of claims 222-235, wherein the treatment of type 2 diabetes mellitus comprises a reduction in HbA1c levels.

237. The method of claim 236, wherein the HbA1c levels are reduced to about or below 5.7 %.

238. The method of any one of claims 222-237, wherein the treatment of type 2 diabetes mellitus comprises a reduction in glucagon levels.

239. The method of any one of claims 222-238, wherein the treatment of type 2 diabetes mellitus comprises an increase in insulin levels.

240. The method of any one of claims 222-239, wherein the treatment of type 2 diabetes mellitus comprises a decrease in BMI.

241. The method of claim 240, wherein the BMI is decreased to about or below 25 kg/m².

242. The method of any of one of claims 222-241, wherein the compound of any one of claims 1-190, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 191, is administered orally.

243. The method of any one of claims 222-242, further comprising administering an additional therapy or therapeutic agent to the patient.

244. The method of claim 243, wherein the additional therapy or therapeutic agent is selected from the group consisting of an anti-diabetic agent, an anti-obesity agent, a GLP-1 receptor agonist, an agent to treat non-alcoholic steatohepatitis (NASH), gastric electrical stimulation, dietary monitoring, physical activity, or any combinations thereof.

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245. The method of claim 244, wherein the anti-diabetic agent is selected from the group consisting of a biguanide, a sulfonylurea, a glitazar, a thiazolidinedione, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a meglitinide, a sodium-glucose linked transporter 2 (SGLT2) inhibitor, a glitazone, a GRP40 agonist, a glucose-dependent insulinotropic peptide (GIP), an insulin or insulin analogue, an alpha glucosidase inhibitor, a sodium-glucose linked transporter 1 (SGLT1) inhibitor, or any combinations thereof.

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246. The method of claim 245, wherein the biguanide is metformin.

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247. The method of claim 244, wherein the anti-obesity agent is selected from the group consisting of neuropeptide Y receptor type 2 (NPYR2) agonist, a NPYR1 or NPYR5 antagonist, a human proislet peptide (HIP), a cannabinoid receptor type 1 (CB1R) antagonist, a lipase inhibitor, a melanocortin receptor 4 agonist, a farnesoid X receptor (FXR) agonist, phentermine, zonisamide, a norepinephrine/dopamine reuptake inhibitor, a GDF-15 analog, an opioid receptor antagonist, a cholecystokinin agonist, a serotonergic agent, a methionine aminopeptidase 2 (MetAP2) inhibitor, diethylpropion, phendimetrazine, benzphetamine, a fibroblast growth factor receptor (FGFR) modulator, an AMP-activated protein kinase (AMPK) activator, a sodium-glucose cotransporter 1 (SGLT-1) inhibitor, or any combinations thereof.

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248. The method of claim 244, wherein the GLP-1 receptor agonist is selected from the group consisting of liraglutide, exenatide, dulaglutide, albiglutide, taspoglutide, lixisenatide, semaglutide, or any combinations thereof.

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249. The method of claim 244, wherein the agent to treat NASH is selected from the group consisting of an FXR agonist, PF-05221304, a synthetic fatty acid-bile conjugate, an anti-lysyl oxidase homologue 2 (LOXL2) monoclonal antibody, a caspase

inhibitor, a MAPK5 inhibitor, a galectin 3 inhibitor, a fibroblast growth factor 21 (FGF21) agonist, a niacin analogue, a leukotriene D4 (LTD4) receptor antagonist, an acetyl-CoA carboxylase (ACC) inhibitor, a ketohexokinase (KHK) inhibitor, an ileal bile acid transporter (IBAT) inhibitor, an apoptosis signal-regulating kinase 1 (ASK1) inhibitor, a
5 peroxisome proliferator-activated receptor (PPAR) agonist, a diacylglycerol acyltransferase 2 (DGAT2) inhibitor, or any combinations thereof.

250. The method of any one of claims 243-249, wherein the compound of any one of claims 1-220 or a pharmaceutically acceptable salt or solvate thereof, or a
10 pharmaceutical composition according to claim 221, and the additional therapeutic agent are administered as separate dosages sequentially in any order.

251. A method for modulating insulin levels in a patient in need of such modulating, the method comprising administering to the patient an effective amount of a
15 compound as claimed in any one of claims 1-220, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 221.

252. The method of claim 251, wherein the modulation results in an increase of insulin levels.

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253. A method for modulating glucose levels in a patient in need of such modulating, the method comprising administering to the patient an effective amount of a compound as claimed in any one of claims 1-220, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 221.

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254. The method of claim 253, wherein the modulation results in a decrease of glucose levels.

255. A method for treating a GLP-1 associated disease, disorder, or condition,
30 the method comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1-220, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 221.

256. The method of claim 255, wherein the disease, disorder, or condition is selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, early onset type 2 diabetes mellitus, idiopathic type 1 diabetes mellitus (Type 1b), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), obesity, weight gain from use of other agents, idiopathic intracranial hypertension, Wolfram syndrome, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, malnutrition-related diabetes, gestational diabetes, kidney disease, adipocyte dysfunction, sleep apnea, visceral adipose deposition, eating disorders, cardiovascular disease, congestive heart failure, myocardial infarction, left ventricular hypertrophy, peripheral arterial disease, stroke, hemorrhagic stroke, ischemic stroke, transient ischemic attacks, atherosclerotic cardiovascular disease, traumatic brain injury, peripheral vascular disease, endothelial dysfunction, impaired vascular compliance, vascular restenosis, thrombosis, hypertension, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resistance, alcohol use disorder, chronic renal failure, metabolic syndrome, syndrome X, smoking cessation, premenstrual syndrome, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, macular degeneration, cataract, glomerulosclerosis, arthritis, osteoporosis, treatment of addiction, cocaine dependence, bipolar disorder/major depressive disorder, skin and connective tissue disorders, foot ulcerations, psoriasis, primary polydipsia, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), ulcerative colitis, inflammatory bowel disease, colitis, irritable bowel syndrome, Crohn's disease, short bowel syndrome, Parkinson's, Alzheimer's disease, impaired cognition, schizophrenia, Polycystic Ovary Syndrome (PCOS), or any combination thereof.

257. The method of claim 256, wherein the disease, disorder, or condition is selected from the group consisting of type 2 diabetes mellitus, early onset type 2 diabetes mellitus, obesity, weight gain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, gestational diabetes, kidney disease, adipocyte dysfunction, sleep apnea, visceral adipose deposition, eating disorders, cardiovascular

disease, congestive heart failure, myocardial infarction, left ventricular hypertrophy, peripheral arterial disease, stroke, hemorrhagic stroke, ischemic stroke, transient ischemic attacks, atherosclerotic cardiovascular disease, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis, hyperinsulinemia, impaired glucose metabolism, insulin
5 resistance, hepatic insulin resistance, alcohol use disorder, chronic renal failure, metabolic syndrome, syndrome X, smoking cessation, premenstrual syndrome, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, bipolar disorder/major depressive disorder, skin and connective tissue disorders, foot ulcerations, psoriasis, primary polydipsia, non-alcoholic steatohepatitis
10 (NASH), non-alcoholic fatty liver disease (NAFLD), short bowel syndrome, Parkinson's disease, Polycystic Ovary Syndrome (PCOS), idiopathic intracranial hypertension, Wolfram syndrome, or any combination thereof.

258. The method of claim 257, wherein the disease, disorder, or condition
15 includes, but is not limited to type 2 diabetes mellitus, early onset type 2 diabetes mellitus, obesity, weight gain from use of other agents, gout, excessive sugar craving, hypertriglyceridemia, dyslipidemia, gestational diabetes, adipocyte dysfunction, visceral adipose deposition, myocardial infarction, peripheral arterial disease, stroke, transient ischemic attacks, hyperglycemia, post-prandial lipemia, metabolic acidosis, ketosis,
20 hyperinsulinemia, impaired glucose metabolism, insulin resistance, hepatic insulin resistance, chronic renal failure, syndrome X, angina pectoris, diabetic nephropathy, impaired glucose tolerance, diabetic neuropathy, diabetic retinopathy, skin and connective tissue disorders, foot ulcerations, idiopathic intracranial hypertension, Wolfram syndrome, or any combination thereof.

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