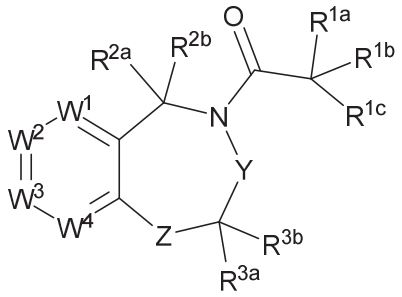
SUMMARY

[0005] In one example, provided herein are compounds that are useful as inhibitors of receptor-interacting protein kinase 1.

[0005a] In one aspect, the present disclosure refers to a compound according to Formula I:



(I),

or a pharmaceutically acceptable salt, solvate, prodrug, isotopic analog, or isomer thereof, wherein

W^1, W^3, and W^4 are CR^7;

W^2 is N or CR^7;

provided that when W^2 is CR^7, then either

a) W^4 is C-CN or

b) R^{1a} is not hydrogen and R^{1b} and R^{1c} together form a piperidinyl ring substituted by $(R^5)_n$ and n is 0-9;

R^{1a}, R^{1b}, and R^{1c} are independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, -OH, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{1d})_2$, $-C(O)R^{1e}$, $-C(O)OR^{1d}$, $-C(O)N(R^{1d})_2$, $-NR^{1d}C(O)R^{1e}$, $-NR^{1d}C(O)N(R^{1d})_2$,$-NR^{1d}C(O)OR^{1d}$, $-OC(O)N(R^{1d})_2$, $-OC(O)OR^{1d}$, $-SR^{1d}$, $-S(O)R^{1e}$, $-S(O)_2R^{1e}$, $-S(O)_3R^{1d}$, $-S(O)N(R^{1d})_2$, $-S(O)_2N(R^{1d})_2$, $-NR^{1d}S(O)R^{1e}$, $-NR^{1d}S(O)_2R^{1e}$, $-NR^{1d}S(O)N(R^{1d})_2$, or $-NR^{1d}S(O)_2N(R^{1d})_2$, wherein each of R^{1a}, R^{1b}, and R^{1c} is optionally and independently substituted with one to eight R^5 and at least one of R^{1a}, R^{1b}, and R^{1c} is other than hydrogen; or

R^{1b} and R^{1c} are optionally taken together to form C_{3-10} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^5; or

R^{1a}, R^{1b}, and R^{1c} are optionally taken together to form C_{5-10} cycloalkyl or 6- to 8-membered heterocyclyl, each of which is optionally substituted with one to eight R^5; or

R^{1a} is absent and R^{1b} and R^{1c} are taken together to form C_{6-10} aryl or 5- to 12-membered heteroaryl, each of which is optionally substituted with one to eight R^5;

each R^{1d} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{1d} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^5;

each R^{1e} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

R^{2a} and R^{2b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, or

R^{2a} and R^{2b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, each of which is optionally substituted with one to eight R^6;

R^{3a} and R^{3b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{3a} and R^{3b} are optionally taken together to form oxo, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6;

Y is O, C(O), S, S(O), $S(O)_2$, $CR^{4a}R^{4b}$, or NR^{4c};

R^{4a} and R^{4b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{4b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{1b} are optionally taken together to form 4- to 12-membered heterocyclyl, which is optionally substituted with one to eight R^6, or

R^{4a} and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6, or

R^{4c} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^5 is independently halogen, -CN, -OH, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, (4- to 12-membered heterocyclyl)(C_{1-8} heteroalkyl), (C_{6-10} aryl)(C_{1-8} heteroalkyl), (5- to 12-membered heteroaryl)(C_{1-8} heteroalkyl), $-N(R^{5a})_2$, $-C(O)R^{5b}$, $-C(O)OR^{5a}$, $-C(O)N(R^{5a})_2$, $-NR^{5a}C(O)R^{5b}$, $-NR^{5a}C(O)N(R^{5a})_2$, $-NR^{5a}C(O)OR^{5a}$, $-OC(O)N(R^{5a})_2$, $-OC(O)OR^{5a}$, $-SR^{5a}$, $-S(O)R^{5b}$, $-S(O)_2R^{5b}$, $-S(O)_3R^{5a}$, $-S(O)N(R^{5a})_2$, $-S(O)_2N(R^{5a})_2$, $-NR^{5a}S(O)R^{5b}$, $-NR^{5a}S(O)_2R^{5b}$, $-NR^{5a}S(O)N(R^{5a})_2$, or $–NR^{5a}S(O)_2N(R^{5a})_2$, each of which is optionally substituted with one to eight R^{5c}, or

two R^5 are optionally taken together to form oxo;

each R^{5a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, and

each R^{5b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl;

each R^{5c} is independently halogen, cyano, C_{1-8} haloalkyl, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, (C_{1-8} alkoxy)(C_{1-8} alkoxy), hydroxyl, SR^{5d}, $N(R^{5d})_2$, $N(R^{5d})_2(C_{1-8}$ alkoxy), C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{5c} are optionally taken together to form oxo;

each R^{5d} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^6 is halogen, -CN, -OH, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{6a})_2$, $-C(O)R^{6b}$, $-C(O)N(R^{6a})_2$, or $-C(O)OR^{6a}$, or

two R^6 are taken together to form oxo;

each R^{6a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl, or

two R^{6a} on the same atom are optionally taken together to form 4- to 6-membered heterocyclyl;

each R^{6b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

each R^7 is independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered

heteroaryl, -OR^{7a}, -$C(O)R^{7b}$, -$N(R^{7a})_2$, -$C(O)OR^{7a}$, -$C(O)N(R^{7a})_2$, -$NR^{7a}C(O)R^{7b}$, -$NR^{7a}C(O)N(R^{7a})_2$,-$NR^{7a}C(O)OR^{7a}$, -$OC(O)N(R^{7a})_2$, -$OC(O)OR^{7a}$,-SR^{7a}, -$S(O)R^{7b}$, -$S(O)_2R^{7b}$, -$S(O)_3R^{7a}$, -$S(O)N(R^{7a})_2$, -$S(O)_2N(R^{7a})_2$, -$NR^{7a}S(O)R^{7b}$, –$NR^{7a}S(O)_2R^{7b}$, -$NR^{7a}S(O)N(R^{7a})_2$, or –$NR^{7a}S(O)_2N(R^{7a})_2$, each of which is optionally and independently substituted with one to eight R^8;

each R^{7a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{7a} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^8;

each R^{7b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^8 is halogen, -CN, -OH, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, -$N(R^{8a})_2$, -$C(O)R^{8b}$, or -$C(O)OR^{8a}$, or

two R^8 are optionally taken together to form oxo;

each R^{8a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^{8b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

Z is $C(R^9)_2$, C(O), O, S, S(O), $S(O)_2$, $S(O)NR^9$, or NR^9;

provided that when Z is N, then R^{3a} and R^{3b} are not oxo;

each R^9 is independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, 4- to 8-membered heterocyclyl, or –$C(O)R^{9a}$; and

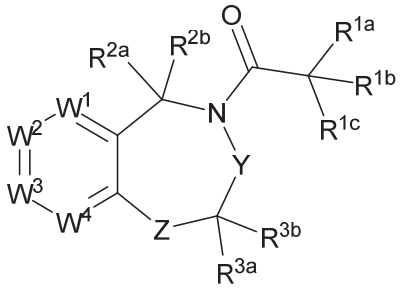
R^{9a} is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, or 4- to 12-membered heterocyclyl, or

R^9 and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6.

[0005b] In one aspect, the present disclosure refers to a compound selected from Table 1 or Examples 258-309, or a pharmaceutically acceptable salt, solvate, prodrug, isotopic analog, or isomer thereof

[0006] In another example provided are methods for making the compounds and intermediates thereof.

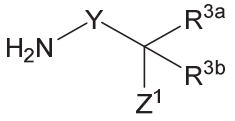
[0006a] In one aspect, the present disclosure refers to a method for preparing a compound according to Formula A:



(A),

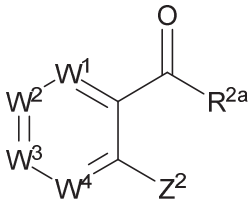
or a salt thereof, the method comprising:

contacting a compound according to Formula IIa



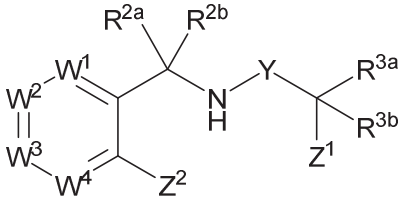
(IIa)

with a compound according to Formula IIb,



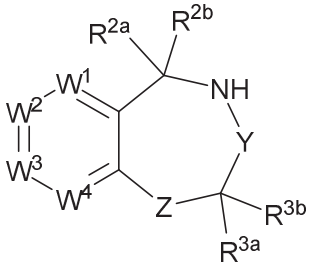
(IIb)

under conditions sufficient to form a compound according to Formula IIc



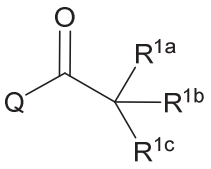
(IIc);

converting the compound of Formula IIc to a compound of Formula IId



(IId); and

contacting the compound of Formula IId with a compound of Formula IIe



(IIe)

under conditions sufficient to form the compound of Formula A;

wherein:

Z^1 is an optionally protected first reactive group;

Z^2 is an optionally protected second reactive group;

Q is -OH or a leaving group; and

W^1, W^2, W^3, and W^4 are independently N or CR^7;

R^{1a}, R^{1b}, and R^{1c} are independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, -OH, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{1d})_2$, $-C(O)R^{1e}$, $-C(O)OR^{1d}$, $-C(O)N(R^{1d})_2$, $-NR^{1d}C(O)R^{1e}$, $-NR^{1d}C(O)N(R^{1d})_2$, $-NR^{1d}C(O)OR^{1d}$, $-OC(O)N(R^{1d})_2$, $-OC(O)OR^{1d}$, $-SR^{1d}$, $-S(O)R^{1e}$, $-S(O)_2R^{1e}$, $-S(O)_3R^{1d}$, $-S(O)N(R^{1d})_2$, $-S(O)_2N(R^{1d})_2$, $-NR^{1d}S(O)R^{1e}$, $-NR^{1d}S(O)_2R^{1e}$, $-NR^{1d}S(O)N(R^{1d})_2$, or $-NR^{1d}S(O)_2N(R^{1d})_2$, wherein each of R^{1a}, R^{1b}, and R^{1c} is optionally and independently substituted with one to eight R^5 and at least one of R^{1a}, R^{1b}, and R^{1c} is other than hydrogen; or

R^{1b} and R^{1c} are optionally taken together to form C_{3-10} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^5; or

R^{1a}, R^{1b}, and R^{1c} are optionally taken together to form C_{5-10} cycloalkyl or 5- to 12-membered heterocyclyl, each which is optionally substituted with one to eight R^5; or

R^{1a} is absent and R^{1b} and R^{1c} are taken together to form C_{6-10} aryl or 5- to 12-membered heteroaryl or 5- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^5;

each R^{1d} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{1d} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^5;

each R^{1e} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

R^{2a} and R^{2b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, or

R^{2a} and R^{2b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, each of which is optionally substituted with one to eight R^6;

R^{3a} and R^{3b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{3a} and R^{3b} are optionally taken together to form oxo, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6;

Y is O, C(O), S, S(O), $S(O)_2$, $CR^{4a}R^{4b}$, or NR^{4c};

R^{4a} and R^{4b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{4b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{1b} are optionally taken together to form 4- to 12-membered heterocyclyl, which is optionally substituted with one to eight R^6, or

R^{4a} and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6, or

R^{4c} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^5 is independently halogen, -CN, -OH, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, (4- to 12-membered heterocyclyl)(C_{1-8} heteroalkyl), (C_{6-10} aryl)(C_{1-8} heteroalkyl), (5- to 12-membered heteroaryl)(C_{1-8} heteroalkyl), $-N(R^{5a})_2$, $-C(O)R^{5b}$, $-C(O)OR^{5a}$, $-C(O)N(R^{5a})_2$, $-NR^{5a}C(O)R^{5b}$, $-NR^{5a}C(O)N(R^{5a})_2$, $-NR^{5a}C(O)OR^{5a}$, $-OC(O)N(R^{5a})_2$, $-OC(O)OR^{5a}$, $-SR^{5a}$, $-S(O)R^{5b}$, $-S(O)_2R^{5b}$, $-S(O)_3R^{5a}$, $-S(O)N(R^{5a})_2$, $-S(O)_2N(R^{5a})_2$, $-NR^{5a}S(O)R^{5b}$, $-NR^{5a}S(O)_2R^{5b}$,

$-NR^{5a}S(O)N(R^{5a})_2$, or $-NR^{5a}S(O)_2N(R^{5a})_2$, each of which is optionally substituted with one to eight R^{5c}, or

two R^5 are optionally taken together to form oxo;

each R^{5a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, and

each R^{5b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl;

each R^{5c} is independently halogen, cyano, C_{1-8} haloalkyl, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, (C_{1-8} alkoxy)(C_{1-8} alkoxy), hydroxyl, SR^{5d}, $N(R^{5d})_2$, $N(R^{5d})_2(C_{1-8}$ alkoxy), C_{3-10} cycloalkyl, and 4- to 12-membered heterocyclyl, or

two R^{5c} are optionally taken together to form oxo;

each R^{5d} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^6 is halogen, -CN, -OH, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{6a})_2$, $-C(O)R^{6b}$, $-C(O)N(R^{6a})_2$, or $-C(O)OR^{6a}$, or

two R^6 are taken together to form oxo;

each R^{6a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl, or

two R^{6a} on the same atom are optionally taken together to form 4- to 6-membered heterocyclyl;

each R^{6b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

each R^7 is independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-OR^{7a}$, $-C(O)R^{7b}$, $-N(R^{7a})_2$, $-C(O)OR^{7a}$, $-C(O)N(R^{7a})_2$, $-NR^{7a}C(O)R^{7b}$, $-NR^{7a}C(O)N(R^{7a})_2$,$-NR^{7a}C(O)OR^{7a}$, $-OC(O)N(R^{7a})_2$, $-OC(O)OR^{7a}$,$-SR^{7a}$, $-S(O)R^{7b}$, $-S(O)_2R^{7b}$, $-S(O)_3R^{7a}$, $-S(O)N(R^{7a})_2$, $-S(O)_2N(R^{7a})_2$, $-NR^{7a}S(O)R^{7b}$, $-NR^{7a}S(O)_2R^{7b}$, $-NR^{7a}S(O)N(R^{7a})_2$, or $-NR^{7a}S(O)_2N(R^{7a})_2$, each of which is optionally and independently substituted with one to eight R^8;

each R^{7a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{7a} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^8;

each R^{7b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^8 is halogen, -CN, -OH, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{8a})_2$, $-C(O)R^{8b}$, or $-C(O)OR^{8a}$, or two R^8 are optionally taken together to form oxo;

each R^{8a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^{8b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

Z is $C(R^9)_2$, C(O), O, S, S(O), $S(O)_2$, $S(O)NR^9$, or NR^9;

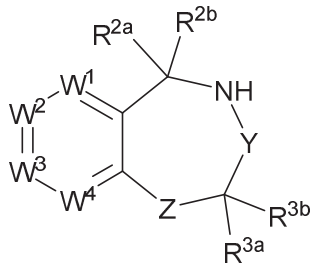
each R^9 is independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, 4- to 8-membered heterocyclyl, or $–C(O)R^{9a}$; and

R^{9a} is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, or 4- to 12-membered heterocyclyl, or

R^9 and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6.

[0007] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable excipient.

[0007a] In one aspect, the present disclosure refers to a compound according to Formula IId,



(IId)

or a salt thereof, wherein

W^1, W^2, W^3, and W^4 are independently N or CR^7;

R^{2a} and R^{2b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, or

R^{2a} and R^{2b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, each of which is optionally substituted with one to eight R^6;

R^{3a} and R^{3b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{3a} and R^{3b} are optionally taken together to form oxo, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6;

Y is O, C(O), S, S(O), $S(O)_2$, $CR^{4a}R^{4b}$, or NR^{4c};

R^{4a} and R^{4b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{4b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{1b} are optionally taken together to form 4- to 12-membered heterocyclyl, which is optionally substituted with one to eight R^6, or

R^{4a} and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6, or

R^{4c} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^6 is halogen, -CN, -OH, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{6a})_2$, $-C(O)R^{6b}$, $-C(O)N(R^{6a})_2$, or $-C(O)OR^{6a}$, or

two R^6 are taken together to form oxo;

each R^{6a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl, or

two R^{6a} on the same atom are optionally taken together to form 4- to 6-membered heterocyclyl;

each R^{6b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

each R^7 is independently hydrogen, halogen, -CN, -N_3, -NO_2, -SF_5, -SCF_3, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, -OR^{7a}, -$C(O)R^{7b}$, -$N(R^{7a})_2$, -$C(O)OR^{7a}$, -$C(O)N(R^{7a})_2$, -$NR^{7a}C(O)R^{7b}$, -$NR^{7a}C(O)N(R^{7a})_2$,-$NR^{7a}C(O)OR^{7a}$, -$OC(O)N(R^{7a})_2$, -$OC(O)OR^{7a}$,-SR^{7a}, -$S(O)R^{7b}$, -$S(O)_2R^{7b}$, -$S(O)_3R^{7a}$, -$S(O)N(R^{7a})_2$, -$S(O)_2N(R^{7a})_2$, -$NR^{7a}S(O)R^{7b}$, –$NR^{7a}S(O)_2R^{7b}$, -$NR^{7a}S(O)N(R^{7a})_2$, or -$NR^{7a}S(O)_2N(R^{7a})_2$, each of which is optionally and independently substituted with one to eight R^8;

each R^{7a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{7a} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^8;

each R^{7b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^8 is halogen, -CN, -OH, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, -$N(R^{8a})_2$, -$C(O)R^{8b}$, or -$C(O)OR^{8a}$, or

two R^8 are optionally taken together to form oxo;

each R^{8a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^{8b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

Z is $C(R^9)_2$, C(O), O, S, S(O), $S(O)_2$, $S(O)NR^9$, or NR^9;

each R^9 is independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, 4- to 8-membered heterocyclyl, or –$C(O)R^{9a}$; and

R^{9a} is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, or 4- to 12-membered heterocyclyl, or

R^9 and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6.

[0008] In another example, provided herein is a method of inhibiting a receptor-interacting protein kinase 1. Further provided are methods for treating a receptor-interacting protein kinase 1-mediated disease or disorder comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition as described herein to a subject in need thereof. The disclosure also provides uses of the compounds or compositions thereof in

the manufacture of a medicament for the treatment of a disease, disorder or condition that is mediated by (or mediated, at least in part, by) receptor-interacting protein kinase.

[0008a] In one aspect, the present disclosure refers to an *in vitro* method of inhibiting receptor-interacting protein kinase 1, the method comprising contacting the receptor-interacting protein kinase 1 with an effective amount of a compound disclosed herein.

[0008b] In one aspect, the present disclosure refers to use of a compound disclosed herein or a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a receptor-interacting protein kinase 1-mediated disease or disorder in a subject in need thereof.

[0008c] In one aspect, the present disclosure refers to use of a compound disclosed herein in the manufacture of a medicament for inhibiting receptor-interacting protein kinase 1 in a subject in need thereof, wherein the receptor-interacting protein kinase 1 is to be contacted with the compound.

DESCRIPTION

I. Definitions

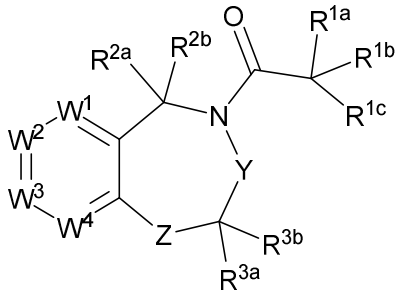
[0009] As used herein, the term "alkyl," by itself or as part of another substituent, refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{1-7}, C_{1-8}, C_{1-9}, C_{1-10}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. For example, C_{1-6} alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can also refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Alkyl groups can be substituted or unsubstituted. Unless otherwise specified, "substituted alkyl" groups can be substituted with one or more halo, hydroxy, amino, alkylamino, amido, acyl, nitro, cyano, and/or alkoxy groups.

[0010] As used herein, the term "alkoxy," by itself or as part of another substituent, refers to a group having the formula -OR, wherein R is alkyl.

[0011] As used herein, the term "cycloalkyl," by itself or as part of another substituent, refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated.

WHAT IS CLAIMED IS:

1. A compound according to Formula I:



(I),

or a pharmaceutically acceptable salt, solvate, prodrug, isotopic analog, or isomer thereof, wherein

W^1, W^3, and W^4 are CR^7;

W^2 is N or CR^7;

provided that when W^2 is CR^7, then either

a) W^4 is C-CN or

b) R^{1a} is not hydrogen and R^{1b} and R^{1c} together form a piperidinyl ring substituted by $(R^5)_n$ and n is 0-9;

R^{1a}, R^{1b}, and R^{1c} are independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, -OH, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{1d})_2$, $-C(O)R^{1e}$, $-C(O)OR^{1d}$, $-C(O)N(R^{1d})_2$, $-NR^{1d}C(O)R^{1e}$, $-NR^{1d}C(O)N(R^{1d})_2$,$-NR^{1d}C(O)OR^{1d}$, $-OC(O)N(R^{1d})_2$, $-OC(O)OR^{1d}$, $-SR^{1d}$, $-S(O)R^{1e}$, $-S(O)_2R^{1e}$, $-S(O)_3R^{1d}$, $-S(O)N(R^{1d})_2$, $-S(O)_2N(R^{1d})_2$, $-NR^{1d}S(O)R^{1e}$, $-NR^{1d}S(O)_2R^{1e}$, $-NR^{1d}S(O)N(R^{1d})_2$, or $-NR^{1d}S(O)_2N(R^{1d})_2$, wherein each of R^{1a}, R^{1b}, and R^{1c} is optionally and independently substituted with one to eight R^5 and at least one of R^{1a}, R^{1b}, and R^{1c} is other than hydrogen; or

R^{1b} and R^{1c} are optionally taken together to form C_{3-10} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^5; or

R^{1a}, R^{1b}, and R^{1c} are optionally taken together to form C_{5-10} cycloalkyl or 6- to 8-membered heterocyclyl, each of which is optionally substituted with one to eight R^5; or

R^{1a} is absent and R^{1b} and R^{1c} are taken together to form C_{6-10} aryl or 5- to 12-membered heteroaryl, each of which is optionally substituted with one to eight R^5;

each R^{1d} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{1d} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^5;

each R^{1e} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

R^{2a} and R^{2b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, or

R^{2a} and R^{2b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, each of which is optionally substituted with one to eight R^6;

R^{3a} and R^{3b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{3a} and R^{3b} are optionally taken together to form oxo, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6;

Y is O, C(O), S, S(O), $S(O)_2$, $CR^{4a}R^{4b}$, or NR^{4c};

R^{4a} and R^{4b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{4b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{1b} are optionally taken together to form 4- to 12-membered heterocyclyl, which is optionally substituted with one to eight R^6, or

R^{4a} and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6, or

R^{4c} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^5 is independently halogen, -CN, -OH, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, (4- to 12-membered heterocyclyl)(C_{1-8} heteroalkyl), (C_{6-10} aryl)(C_{1-8} heteroalkyl), (5- to 12-membered heteroaryl)(C_{1-8} heteroalkyl), $-N(R^{5a})_2$, $-C(O)R^{5b}$, $-C(O)OR^{5a}$, $-C(O)N(R^{5a})_2$, $-NR^{5a}C(O)R^{5b}$, $-NR^{5a}C(O)N(R^{5a})_2$, $-NR^{5a}C(O)OR^{5a}$, $-OC(O)N(R^{5a})_2$, $-OC(O)OR^{5a}$, $-SR^{5a}$, $-S(O)R^{5b}$, $-S(O)_2R^{5b}$, $-S(O)_3R^{5a}$, $-S(O)N(R^{5a})_2$, $-S(O)_2N(R^{5a})_2$, $-NR^{5a}S(O)R^{5b}$, $-NR^{5a}S(O)_2R^{5b}$, $-NR^{5a}S(O)N(R^{5a})_2$, or $-NR^{5a}S(O)_2N(R^{5a})_2$, each of which is optionally substituted with one to eight R^{5c}, or

two R^5 are optionally taken together to form oxo;

each R^{5a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, and

each R^{5b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl;

each R^{5c} is independently halogen, cyano, C_{1-8} haloalkyl, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, (C_{1-8} alkoxy)(C_{1-8} alkoxy), hydroxyl, SR^{5d}, $N(R^{5d})_2$, $N(R^{5d})_2(C_{1-8}$ alkoxy), C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{5c} are optionally taken together to form oxo;

each R^{5d} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^6 is halogen, -CN, -OH, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{6a})_2$, $-C(O)R^{6b}$, $-C(O)N(R^{6a})_2$, or $-C(O)OR^{6a}$, or

two R^6 are taken together to form oxo;

each R^{6a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl, or

two R^{6a} on the same atom are optionally taken together to form 4- to 6-membered heterocyclyl;

each R^{6b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

each R^7 is independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered

heteroaryl, -OR^{7a}, -$C(O)R^{7b}$, -$N(R^{7a})_2$, -$C(O)OR^{7a}$, -$C(O)N(R^{7a})_2$, -$NR^{7a}C(O)R^{7b}$, -$NR^{7a}C(O)N(R^{7a})_2$,-$NR^{7a}C(O)OR^{7a}$, -$OC(O)N(R^{7a})_2$, -$OC(O)OR^{7a}$,-SR^{7a}, -$S(O)R^{7b}$, -$S(O)_2R^{7b}$, -$S(O)_3R^{7a}$, -$S(O)N(R^{7a})_2$, -$S(O)_2N(R^{7a})_2$, -$NR^{7a}S(O)R^{7b}$, –$NR^{7a}S(O)_2R^{7b}$, -$NR^{7a}S(O)N(R^{7a})_2$, or –$NR^{7a}S(O)_2N(R^{7a})_2$, each of which is optionally and independently substituted with one to eight R^8;

each R^{7a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{7a} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^8;

each R^{7b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^8 is halogen, -CN, -OH, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, -$N(R^{8a})_2$, -$C(O)R^{8b}$, or -$C(O)OR^{8a}$, or

two R^8 are optionally taken together to form oxo;

each R^{8a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^{8b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

Z is $C(R^9)_2$, C(O), O, S, S(O), $S(O)_2$, $S(O)NR^9$, or NR^9;

provided that when Z is N, then R^{3a} and R^{3b} are not oxo;

each R^9 is independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, 4- to 8-membered heterocyclyl, or –$C(O)R^{9a}$; and

R^{9a} is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, or 4- to 12-membered heterocyclyl, or

R^9 and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6.

2. A compound of claim 1, wherein W^2 is N.

3. A compound of claim 2, wherein

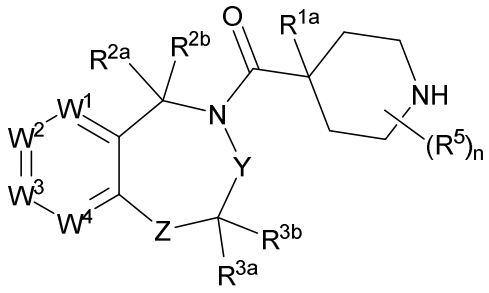
Z is O;

Y is $CR^{4a}R^{4b}$;

R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, and R^{4b} are H; and

R^{1a}, R^{1b}, R^{1c}, R^5, R^7, and R^8 are as defined for Formula I.

4. A compound of claim 1, according to Formula Ia:



(Ia)

wherein

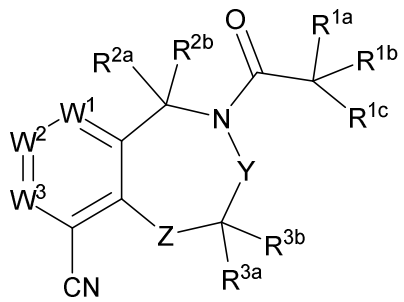
R^{1a}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^5, R^7, W^1, W^2, W^3, W^4, Y, and Z are as defined for Formula I; and

n is 0-9;

provided that when W^1, W^2, W^3, and W^4 are CR^7, then R^{1a} is not hydrogen.

5. A compound of claim 4, wherein at least one of R^5 is attached to the piperidine nitrogen atom.

6. A compound of claim 1, according to Formula Ib:



(Ib),

wherein R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, W^1, W^2, W^3, Y, and Z are as defined for Formula I.

7. A compound of any one of the preceding claims, wherein W^2 is N and W^1, W^3, W^4 are CR^7.

8. A compound of any one of the preceding claims, wherein W^2 is N and W^3 is CH.

9. A compound of any one of the preceding claims, wherein W^2 is N and each R^7 is independently hydrogen, halogen, cyano, C_{1-8} alkyl, C_{1-8} haloalkyl, or C_{1-8} alkoxy.

10. A compound of any one of the preceding claims, wherein W^2 is CR^7.

11. A compound of any one of the preceding claims, wherein each R^7 is independently hydrogen, halogen, cyano, C_{1-8} alkyl, C_{1-8} haloalkyl, or C_{1-8} alkoxy.

12. A compound of any one of the preceding claims, wherein at least one R^7 is halo, C_{1-6} alkyl, C_{1-6} alkoxy, or cyano.

13. A compound of any one of the preceding claims, wherein at least one R^7 is chloro, fluoro, methyl, methoxy, cyano, or bromo.

14. A compound of any one of the preceding claims, wherein one or two of R^7 is 7-chloro, 7-methyl, 8-methoxy, 9-fluoro, 6-fluoro, 6-fluoro-9-cyano, 7-fluoro-9-cyano, 9-cyano, 6-cyano, 8-cyano, 7-fluoro-, or 9-bromo-7-fluoro-.

15. A compound of any one of the preceding claims, wherein W^1 is CH, CF, or CCN.

16. A compound of any one of the preceding claims, wherein W^2 is CH, CCl, CF, or CCH_3.

17. A compound of any one of the preceding claims, wherein W^3 is CH, $COCH_3$, CCN, CF, CCl, or CCF_3.

18. A compound of any one of the preceding claims, wherein W^4 is CH, CCN, CF, Br, Cl, CCl, or CCF_3.

19. A compound of any one of the preceding claims, wherein Z is CH_2.

20. A compound of any one of the preceding claims, wherein Z is O.

21. A compound of any one of the preceding claims, wherein Y is $CR^{4a}R^{4b}$.

22. A compound of any one of the preceding claims, wherein Y is O.

23. A compound of any one of the preceding claims, wherein R^{1a} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, or C_{3-8} cycloalkyl, each of which is optionally substituted with halogen and -CN.

24. A compound of any one of the preceding claims, wherein R^{1b} and R^{1c} are independently C_{1-8} alkyl, C_{1-8} haloalkyl, or C_{3-8} cycloalkyl, each of which is optionally substituted with halogen and -CN.

25. A compound of any one of the preceding claims, wherein at least one of R^{1a}, R^{1b}, and R^{1c} is chloro, methyl, $-CD_3$, ethyl, difluoromethyl, cyanomethyl, cyclopropyl, cyclopropylmethyl, trifluoromethyl, methoxy, trifluoromethoxymethyl, 2,2,2-trifluoroethyl, 1,1-difluoroethyl, 2-fluoroethyl, trifluoromethoxy, 1-cyanoethyl, fluoromethyl, 1-hydroxycyclopropyl, difluoromethylcyclopropyl, cyanocyclopropyl, 3,3-difluorocyclobutyl, 1,1,2,2,2-pentafluoroethyl, 1-methylethyl, methylsulfanyl, methoxymethyl, 5-fluoropyrimidin-2-ylsulfanyl, azetidin-3-yl, pyrroldin-3-yl, cyano, or hydroxyl.

26. A compound of any one of the preceding claims, wherein R^{1b} and R^{1c} are taken together to form 4- to 12-membered heterocyclyl, which is optionally substituted with one to eight R^5.

27. A compound of any one of the preceding claims, wherein R^{1b} and R^{1c} are taken together to form a 4, 5, 6, or 7 membered heterocyclyl containing a nitrogen ring atom and optionally substituted with one to eight R^5.

28. A compound of claim 26 or claim 27, wherein the heterocyclyl is substituted with one to four R^5.

29. A compound of any one of the preceding claims, wherein at least one of R^5 is C_{1-8} alkyl, C_{1-8} haloalkyl, halogen, C_{1-8} haloalkyl, C_{1-8} alkoxy, -OH, or cyano.

30. A compound of any one of the preceding claims, wherein at least one of R^5 is methyl, ethyl, fluoro, chloro, difluoromethyl, fluoromethyl, methoxy, hydroxyl, C_{1-8} haloalkyl, halogen, C_{1-8} haloalkyl, C_{1-8} alkoxy, or cyano.

31. A compound of any one of the preceding claims, wherein at least one of R^5 is 4- to 12-membered heterocyclyl or 5- to 12-membered heteroaryl, each of which is optionally substituted with one to eight R^{5c}.

32. A compound of claim 31, wherein at least one of R^5 is a 5- to 12-membered heteroaryl optionally substituted with one to eight R^{5c}.

33. A compound of claim 32, wherein the 5- to 12-membered heteroaryl is selected from pyrimidin-2-yl, pyrimidin-4-yl, pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-8-yl, [1,2,4]triazolo[1,5-c]pyrimidin-5-yl, pyrazolo[1,5-a][1,3,5]triazin-4-yl, pyrazolo[1,5-a]pyrimidin-7-yl, pyridazin-4-yl, quinazolin-2-yl, imidazo[1,2-a]pyrazin-8-yl, pyrazolo[4,3-c]pyridin-6-yl, pyrrolo[3,2-d]pyrimidin-2-yl, imidazo[1,2-b]pyridazin-6-yl, pyrazolo[1,5-a]pyrimidin-7-yl, 6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl, pyrid-2-yl, pyrid-3-yl, methoxypyridazin-3-yl, 5,7-dihydrofuro[3,4-d]pyrimidin-2-yl, purin-2-yl, quinazolin-2-yl, quinoxalin-2-yl, isoquinol-3-yl, quinol-2-yl, and 1,3,5-triazin-2-yl, and imidazo[2,1-f][1,2,4]triazin-4-yl, each of which is optionally substituted with one to eight R^{5c}.

34. A compound of claims 32 or 33, wherein the heterocyclyl is substituted with one to three R^{5c}.

35. A compound of claim 34, wherein R^{5c} is independently fluoro, methoxy, difluoromethoxy, methyl, methylamino, cyclopropylamino, 2,2-difluoroethoxy, methylsulfanyl, dimethylaminopropoxy, chloro, 2-methoxyethoxy, dimethylaminoethoxy, cyano, trifluoromethyl, ethoxy, difluoromethyl, cyclopropyl, and oxo.

36. A compound of any one of the preceding claims, wherein R^{1b} and R^{1c} are taken together to form 2,2-difluorocycobutyl, 3,3-difluorocycobutyl, (5-fluoropyrimidin-2-yl)piperidin-4-yl, tetrahydopyran-4-yl, tetrahydopyran-3-yl, tetrahydofuran-3-yl, cylcopropyl, or cyclobutyl.

37. A compound of any one of the preceding claims, wherein R^{1a} is hydrogen.

38. A compound of any one of the preceding claims, wherein R^{1a} is chloro, fluoro, methyl, ethyl, difluoromethyl, fluoromethyl, cyano, or hydroxyl.

39. A compound of any one of the preceding claims, wherein R^{1a}, R^{1b}, and R^{1c} are taken together to form bicyclo[1.1.1]pentane, azabicyclo[4.1.0]heptane, azepan-4yl, 1,4-oxepane-7-yl, tetrahydropyran-2-yl, or 3,6-dihydro-2H-pyridin-4-yl.

40. A compound of any one of the preceding claims, wherein R^{2a} is hydrogen and R^{2b} is $C_{1\text{-}8}$ alkyl.

41. A compound of any one of the preceding claims, wherein R^{2a} and R^{2b} are hydrogen.

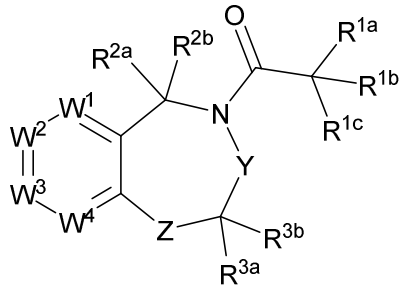
42. A compound of any one of the preceding claims, wherein R^{4a} is hydrogen or methyl.

43. A compound of any one of the preceding claims, wherein R^{3a} and R^{3b} are independently hydrogen or methyl.

44. A compound selected from Table 1 or Examples 258-309, or a pharmaceutically acceptable salt, solvate, prodrug, isotopic analog, or isomer thereof.

45. A pharmaceutical composition comprising a compound according to any one of claims 1-44, and a pharmaceutically acceptable excipient.

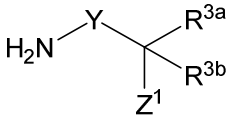
46. A method for preparing a compound according to Formula A:



(A),

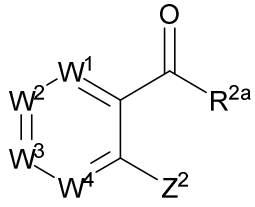
or a salt thereof, the method comprising:

contacting a compound according to Formula IIa



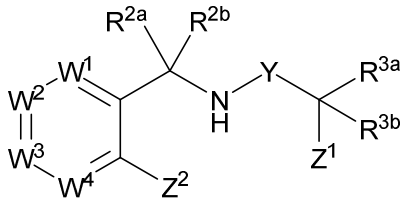
(IIa)

with a compound according to Formula IIb,



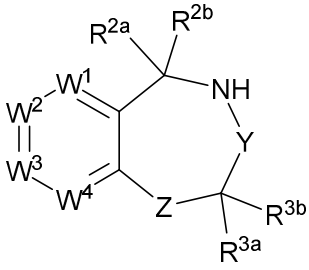
(IIb)

under conditions sufficient to form a compound according to Formula IIc



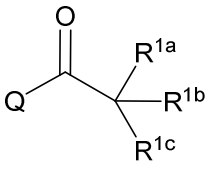
(IIc);

converting the compound of Formula IIc to a compound of Formula IId



(IId); and

contacting the compound of Formula IId with a compound of Formula IIe



(IIe)

under conditions sufficient to form the compound of Formula A;

wherein:

Z^1 is an optionally protected first reactive group;

Z^2 is an optionally protected second reactive group;

Q is -OH or a leaving group; and

W^1, W^2, W^3, and W^4 are independently N or CR^7;

R^{1a}, R^{1b}, and R^{1c} are independently hydrogen,

halogen, -CN, -N_3, -NO_2, -OH, -SF_5, -SCF_3, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, -$N(R^{1d})_2$, -$C(O)R^{1e}$, -$C(O)OR^{1d}$, -$C(O)N(R^{1d})_2$, -$NR^{1d}C(O)R^{1e}$, -$NR^{1d}C(O)N(R^{1d})_2$, -$NR^{1d}C(O)OR^{1d}$, -$OC(O)N(R^{1d})_2$, -$OC(O)OR^{1d}$, -SR^{1d}, -$S(O)R^{1e}$, -$S(O)_2R^{1e}$, -$S(O)_3R^{1d}$, -$S(O)N(R^{1d})_2$,

$-S(O)_2N(R^{1d})_2$, $-NR^{1d}S(O)R^{1e}$, $-NR^{1d}S(O)_2R^{1e}$, $-NR^{1d}S(O)N(R^{1d})_2$, or $-NR^{1d}S(O)_2N(R^{1d})_2$, wherein each of R^{1a}, R^{1b}, and R^{1c} is optionally and independently substituted with one to eight R^5 and at least one of R^{1a}, R^{1b}, and R^{1c} is other than hydrogen; or

R^{1b} and R^{1c} are optionally taken together to form C_{3-10} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^5; or

R^{1a}, R^{1b}, and R^{1c} are optionally taken together to form C_{5-10} cycloalkyl or 5- to 12-membered heterocyclyl, each which is optionally substituted with one to eight R^5; or

R^{1a} is absent and R^{1b} and R^{1c} are taken together to form C_{6-10} aryl or 5- to 12-membered heteroaryl or 5- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^5;

each R^{1d} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{1d} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^5;

each R^{1e} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

R^{2a} and R^{2b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, or

R^{2a} and R^{2b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, each of which is optionally substituted with one to eight R^6;

R^{3a} and R^{3b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{3a} and R^{3b} are optionally taken together to form oxo, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6;

Y is O, C(O), S, S(O), $S(O)_2$, $CR^{4a}R^{4b}$, or NR^{4c};

R^{4a} and R^{4b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl,

wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{4b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{1b} are optionally taken together to form 4- to 12-membered heterocyclyl, which is optionally substituted with one to eight R^6, or

R^{4a} and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6, or

R^{4c} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^5 is independently halogen, -CN, -OH, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, (4- to 12-membered heterocyclyl)(C_{1-8} heteroalkyl), (C_{6-10} aryl)(C_{1-8} heteroalkyl), (5- to 12-membered heteroaryl)(C_{1-8} heteroalkyl), $-N(R^{5a})_2$, $-C(O)R^{5b}$, $-C(O)OR^{5a}$, $-C(O)N(R^{5a})_2$, $-NR^{5a}C(O)R^{5b}$, $-NR^{5a}C(O)N(R^{5a})_2$, $-NR^{5a}C(O)OR^{5a}$, $-OC(O)N(R^{5a})_2$, $-OC(O)OR^{5a}$, $-SR^{5a}$, $-S(O)R^{5b}$, $-S(O)_2R^{5b}$, $-S(O)_3R^{5a}$, $-S(O)N(R^{5a})_2$, $-S(O)_2N(R^{5a})_2$, $-NR^{5a}S(O)R^{5b}$, $-NR^{5a}S(O)_2R^{5b}$, $-NR^{5a}S(O)N(R^{5a})_2$, or $–NR^{5a}S(O)_2N(R^{5a})_2$, each of which is optionally substituted with one to eight R^{5c}, or

two R^5 are optionally taken together to form oxo;

each R^{5a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, and

each R^{5b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl;

each R^{5c} is independently halogen, cyano, C_{1-8} haloalkyl, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, (C_{1-8} alkoxy)(C_{1-8} alkoxy), hydroxyl, SR^{5d}, $N(R^{5d})_2$, $N(R^{5d})_2(C_{1-8}$ alkoxy), C_{3-10} cycloalkyl, and 4- to 12-membered heterocyclyl, or

two R^{5c} are optionally taken together to form oxo;

each R^{5d} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^6 is halogen, -CN, -OH, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{6a})_2$, $-C(O)R^{6b}$, $-C(O)N(R^{6a})_2$, or $-C(O)OR^{6a}$, or

two R^6 are taken together to form oxo;

each R^{6a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl, or

two R^{6a} on the same atom are optionally taken together to form 4- to 6-membered heterocyclyl;

each R^{6b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

each R^7 is independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-OR^{7a}$, $-C(O)R^{7b}$, $-N(R^{7a})_2$, $-C(O)OR^{7a}$, $-C(O)N(R^{7a})_2$, $-NR^{7a}C(O)R^{7b}$, $-NR^{7a}C(O)N(R^{7a})_2$,$-NR^{7a}C(O)OR^{7a}$, $-OC(O)N(R^{7a})_2$, $-OC(O)OR^{7a}$,$-SR^{7a}$, $-S(O)R^{7b}$, $-S(O)_2R^{7b}$, $-S(O)_3R^{7a}$, $-S(O)N(R^{7a})_2$, $-S(O)_2N(R^{7a})_2$, $-NR^{7a}S(O)R^{7b}$, $–NR^{7a}S(O)_2R^{7b}$, $-NR^{7a}S(O)N(R^{7a})_2$, or $-NR^{7a}S(O)_2N(R^{7a})_2$, each of which is optionally and independently substituted with one to eight R^8;

each R^{7a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{7a} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^8;

each R^{7b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^8 is halogen, -CN, -OH, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{8a})_2$, $-C(O)R^{8b}$, or $-C(O)OR^{8a}$, or

two R^8 are optionally taken together to form oxo;

each R^{8a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^{8b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

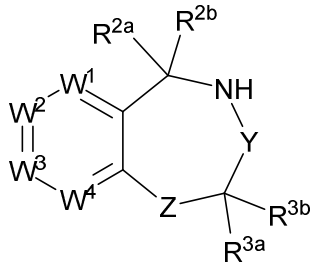
Z is $C(R^9)_2$, C(O), O, S, S(O), $S(O)_2$, $S(O)NR^9$, or NR^9;

each R^9 is independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, 4- to 8-membered heterocyclyl, or $–C(O)R^{9a}$; and

R^{9a} is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, or 4- to 12-membered heterocyclyl, or

R^9 and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6.

47. A compound according to Formula IId,



(IId)

or a salt thereof, wherein

W^1, W^2, W^3, and W^4 are independently N or CR^7;

R^{2a} and R^{2b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl, or

R^{2a} and R^{2b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, each of which is optionally substituted with one to eight R^6;

R^{3a} and R^{3b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{3a} and R^{3b} are optionally taken together to form oxo, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6;

Y is O, C(O), S, S(O), $S(O)_2$, $CR^{4a}R^{4b}$, or NR^{4c};

R^{4a} and R^{4b} are independently hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{4b} are optionally taken together to form C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl, wherein said cycloalkyl and said heterocyclyl are optionally substituted with one to eight R^6, or

R^{4a} and R^{1b} are optionally taken together to form 4- to 12-membered heterocyclyl, which is optionally substituted with one to eight R^6, or

R^{4a} and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6, or

R^{4c} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^6 is halogen, -CN, -OH, C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{6a})_2$, $-C(O)R^{6b}$, $-C(O)N(R^{6a})_2$, or $-C(O)OR^{6a}$, or

two R^6 are taken together to form oxo;

each R^{6a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl, or

two R^{6a} on the same atom are optionally taken together to form 4- to 6-membered heterocyclyl;

each R^{6b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

each R^7 is independently hydrogen, halogen, -CN, $-N_3$, $-NO_2$, $-SF_5$, $-SCF_3$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-OR^{7a}$, $-C(O)R^{7b}$, $-N(R^{7a})_2$, $-C(O)OR^{7a}$, $-C(O)N(R^{7a})_2$, $-NR^{7a}C(O)R^{7b}$, $-NR^{7a}C(O)N(R^{7a})_2$,$-NR^{7a}C(O)OR^{7a}$, $-OC(O)N(R^{7a})_2$, $-OC(O)OR^{7a}$,$-SR^{7a}$, $-S(O)R^{7b}$, $-S(O)_2R^{7b}$, $-S(O)_3R^{7a}$, $-S(O)N(R^{7a})_2$, $-S(O)_2N(R^{7a})_2$, $-NR^{7a}S(O)R^{7b}$, $–NR^{7a}S(O)_2R^{7b}$, $-NR^{7a}S(O)N(R^{7a})_2$, or $-NR^{7a}S(O)_2N(R^{7a})_2$, each of which is optionally and independently substituted with one to eight R^8;

each R^{7a} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl, or

two R^{7a} on the same atom are optionally taken together to form a 4- to 8-membered heterocyclyl optionally substituted by oxo, halo, or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to eight R^8;

each R^{7b} is independently C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl, or 4- to 12-membered heterocyclyl;

each R^8 is halogen, -CN, -OH, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} heteroalkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, 4- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 12-membered heteroaryl, $-N(R^{8a})_2$, $-C(O)R^{8b}$, or $-C(O)OR^{8a}$, or two R^8 are optionally taken together to form oxo;

each R^{8a} is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

each R^{8b} is independently C_{1-8} alkyl or C_{1-8} haloalkyl;

Z is $C(R^9)_2$, C(O), O, S, S(O), $S(O)_2$, $S(O)NR^9$, or NR^9;

each R^9 is independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, 4- to 8-membered heterocyclyl, or $–C(O)R^{9a}$; and

R^{9a} is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, or 4- to 12-membered heterocyclyl, or R^9 and R^{3a} are optionally taken together to form C_{3-8} cycloalkyl or 4- to 12-membered heterocyclyl, each of which is optionally substituted with one to eight R^6.

48. An *in vitro* method of inhibiting receptor-interacting protein kinase 1, the method comprising contacting the receptor-interacting protein kinase 1 with an effective amount of a compound according to any one of claims 1-44.

49. Use of a compound according to any one of claims 1-44 or a pharmaceutical composition according to claim 45 in the manufacture of a medicament for treating a receptor-interacting protein kinase 1-mediated disease or disorder in a subject in need thereof.

50. The use of claim 49, wherein the receptor-interacting protein kinase 1-mediated disease or disorder is necrotizing enterocolitis, tuberous sclerosis, Tangier's Disease, Wohlman's Syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, psoriasis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis (*e.g.,* acute pancreatitis), atopic dermatitis, rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, gout, SoJIA, systemic lupus erythematosus, Sjogren's syndrome, systemic scleroderma, anti-phospholipid syndrome, vasculitis, osteoarthritis, non-alcohol steatohepatitis, alcohol steatohepatitis, autoimmune hepatitis autoimmune hepatobiliary diseases, primary sclerosing cholangitis, nephritis, Celiac disease, autoimmune ITP, transplant rejection, ischemia, ischemia reperfusion injury of solid organs, cerebral ischemia, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial infarction, Huntington's disease, Alzheimer's disease, Parkinson's disease, allergic diseases, asthma, atopic dermatitis, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converting enzyme associated fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor-associated periodic syndrome, periodontitis, infection, bacterial infection, staphylococcus infection, mycobacterium infection, influenza, transplant rejection, burns, hypoxia, trauma, stroke, cardiac infarction, lysosomal storage disease, Niemann-Pick disease, Gaucher's disease, Krabbe disease, amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease), HIV-associated dementia, encephalopathy, retinal degenerative disease, glaucoma, age-related macular degeneration, Friedreich's ataxia, Lewy body disease, diabetic neuropathy, polyglutamine (polyQ) diseases, Fahr disease, Menke's disease, Wilson's disease, a prion disorder, atherosclerosis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, major depressive disorder, bipolar disorder, delirium, post-operative cognitive impairment, autism, schizophrenia, or hidradenitis suppurativa.

51. Use of a compound according to any one of claims 1-44 in the manufacture of a medicament for inhibiting receptor-interacting protein kinase 1 in a subject in need thereof, wherein the receptor-interacting protein kinase 1 is to be contacted with the compound.