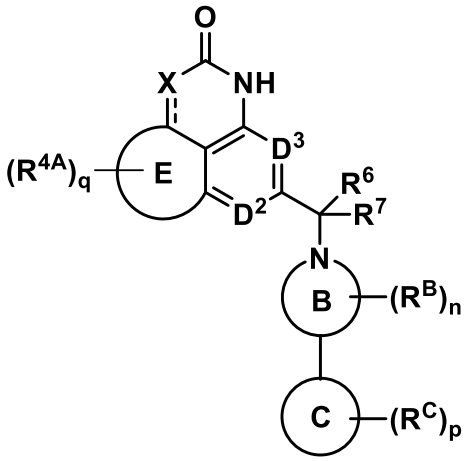
WHAT IS CLAIMED IS:

1. A compound is of Formula VIII:



VIII

or a pharmaceutically acceptable salt thereof, wherein:

----- is a single or double bond;

X is -N(R^a)-;

R^a is hydrogen or -L^{R3}-R^3;

L^{R3} is a covalent bond or a bivalent C_{1-6} aliphatic, wherein the bivalent C_{1-6} aliphatic is optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents;

R^3 is selected from hydrogen, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered bicyclic aryl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered bicyclic aryl, 3- to 7-membered saturated or

partially unsaturated monocyclic heterocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and 8- to 10-membered bicyclic heteroaryl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents;

Ring E is selected from phenyl and 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; q is 0, 1, 2, 3, or 4;

R^6 and R^7 are each independently is hydrogen, deuterium, or C_{1-6} aliphatic wherein the C_{1-6} aliphatic is optionally substituted with 1, 2, 3, or 4 independently selected R^{6A} substituents;

D^2 is C-L^{D2}-R^9 or N;

D^3 is CR^{10} or N;

L^{D2} is a covalent bond or a bivalent C_{1-6} aliphatic, wherein the bivalent C_{1-6} aliphatic is optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents;

R^9 and R^{10} are each independently selected from hydrogen, halogen, -CN, -OR, -SR, -$N(R)_2$, -NO_2, -C(O)R', -C(O)OR, -C(O)$N(R)_2$, -OC(O)R', -OC(O)$N(R)_2$, -OC(O)OR, -OSO_2R', -$OSO_2N(R)_2$, -N(R)C(O)R', -N(R)SO_2R', -S(O)R', -SO_2R', -$SO_2N(R)_2$, -SO_3R', -NHOR, -C(O)NR(OR), -NRC(O)OR, -NRC(O)$N(R)_2$, -NRS(O)$N(R)_2$, -NRS(O)R', -NRS$(O)_2N(R)_2$, -S(O)$N(R)_2$, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 8-membered saturated or partially unsaturated bicyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 8-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 8-membered saturated or partially unsaturated bicyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, and 6- to 8-membered saturated or partially unsaturated bicyclic heterocyclyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{9A} substituents;

Ring B is 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 9- to 16-membered saturated or partially unsaturated polycyclic heterocyclylene having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is phenyl, 8- to 10-membered bicyclic aryl, 10- to 14-membered polycyclic aryl, 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 10- to 16-membered polycyclic heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^B is independently $-L^{RB}-R^{11}$;

each L^{RB} is independently a covalent bond or a bivalent C_{1-6} aliphatic, wherein the bivalent C_{1-6} aliphatic is optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents;

each R^C is independently $-L^{RC}-R^{12}$;

each L^{RC} is independently a covalent bond or a bivalent C_{1-6} aliphatic, wherein the bivalent C_{1-6} aliphatic is optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents;

R^{11} and R^{12} are each independently selected from halogen, =O, -CN, -OR, -SR, $-N(R)_2$, $-N^+(R)_3$, $-NO_2$, -C(O)R', -C(O)OR, $-C(O)N(R)_2$, -OC(O)R', $-OC(O)N(R)_2$, -OC(O)OR, $-OSO_2R'$, $-OSO_2N(R)_2$, -N(R)C(O)R', $-N(R)SO_2R'$, -S(O)R', $-SO_2R'$, $-SO_2N(R)_2$, $-SO_3R'$, -NHOR, -C(O)NR(OR), -NRC(O)OR, $-NRC(O)N(R)_2$, $-C(=NR^m)R'$, $-C(=NR^m)N(R)_2$, $-NRC(=NR^m)N(R)_2$, $-NRC(=NR^m)R'$, $-NRS(O)N(R)_2$, -NRS(O)R', $-NRS(O)(=NR^m)R'$, $-NRS(O)_2N(R)_2$, $-S(O)N(R)_2$, $-OS(O)(=R^m)R'$, $-S(O)(=NR^m)R'$, $-P(O)(R)_2$, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered

bicyclic aryl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 6-membered monocyclic heteroaryl having
1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered bicyclic aryl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and 8- to 10-membered bicyclic heteroaryl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{11A} substituents; or

a R^B and a R^C are taken together with their intervening atoms to form Ring D fused with one or both of Ring B and Ring C, wherein

Ring D is selected from 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 8-membered saturated or partially unsaturated bicyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 8-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 8-membered saturated or partially unsaturated bicyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, 6- to 8-membered saturated or partially unsaturated bicyclic heterocyclyl, phenyl, and 5- to 6-membered monocyclic heteroaryl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{D1} substituents;

each R is independently selected from hydrogen, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to

10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered bicyclic aryl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered bicyclic aryl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and 8- to 10-membered bicyclic heteroaryl are each optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents; or

two R when attached to the same nitrogen atom are taken together to form a 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl is optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents;

each R' is independently selected from C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered bicyclic aryl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein

the C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, phenyl, 8- to 10-membered bicyclic aryl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and 8- to 10-membered bicyclic heteroaryl are each optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents; or

two R' when attached to the same nitrogen atom are taken together to a 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl is optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents;

each R^{3A}, R^{4A}, R^{6A}, R^{9A}, R^{11A}, R^{D1}, and R^N is independently selected from halogen, $–(CH_2)_{0–4}R°$, $–(CH_2)_{0–4}OR°$, $-O(CH_2)_{0-4}R^o$, $–O–(CH_2)_{0–4}C(O)OR°$, $–(CH_2)_{0–4}CH(OR°)_2$, $–(CH_2)_{0–4}SR°$, $–(CH_2)_{0–4}Ph$, $–(CH_2)_{0–4}O(CH_2)_{0–1}Ph$, –CH=CHPh, $–(CH_2)_{0–4}O(CH_2)_{0–1}$-pyridyl, $–NO_2$, –CN, $–N_3$, $-(CH_2)_{0–4}N(R°)_2$, $–(CH_2)_{0–4}N(R°)C(O)R°$, $–N(R°)C(S)R°$, $–(CH_2)_{0–4}N(R°)C(O)NR°_2$, $-N(R°)C(S)NR°_2$, $–(CH_2)_{0–4}N(R°)C(O)OR°$, $-N(R°)N(R°)C(O)R°$, $-N(R°)N(R°)C(O)NR°_2$, $-N(R°)N(R°)C(O)OR°$, $–(CH_2)_{0–4}C(O)R°$, $–C(S)R°$, $–(CH_2)_{0–4}C(O)OR°$, $–(CH_2)_{0–4}C(O)SR°$, $-(CH_2)_{0–4}C(O)OSiR°_3$, $–(CH_2)_{0–4}OC(O)R°$, $–OC(O)(CH_2)_{0–4}SR°$, $–(CH_2)_{0–4}SC(O)R°$, $–(CH_2)_{0–4}C(O)NR°_2$, $–C(S)NR°_2$, $–C(S)SR°$, $–SC(S)SR°$, $-(CH_2)_{0–4}OC(O)NR°_2$, $-C(O)N(OR°)R°$, $–C(O)C(O)R°$, $–C(O)CH_2C(O)R°$, $–C(NOR°)R°$, $-(CH_2)_{0–4}SSR°$, $–(CH_2)_{0–4}S(O)_2R°$, $–(CH_2)_{0–4}S(O)(=NR^o)R°$, $–(CH_2)_{0–4}S(O)_2OR°$, $–(CH_2)_{0–4}OS(O)_2R°$, $–(CH_2)_{0-4}–S(O)_2NR°_2$, $–(CH_2)_{0-4}S(O)(=NR^o)NR°_2$, $-(CH_2)_{0–4}S(O)R°$, $-N(R°)S(O)_2NR°_2$, $–N(R°)S(O)_2R°$, $–N(R°)S(O)(=NR^o)R°$, $–N(OR°)R°$, $–C(NH)NR°_2$, $–P(O)_2R°$, $-P(O)R°_2$, $-OP(O)R°_2$, $–OP(O)(OR°)_2$, $–SiR°_3$, $–(C_{1–4}$ straight or branched alkylene)O–$N(R°)_2$, and $–(C_{1–4}$ straight or branched alkylene)C(O)O–$N(R°)_2$;

each R° is independently hydrogen, $C_{1–6}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, $–CH_2–$(5- to 6-membered heteroaryl ring), or a 3- to 6-membered saturated, partially

unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or two independent occurrences of R°, taken together with their intervening atoms, form a 3- to 12-membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^m is independently –OH, -CN, or R;

n is 0, 1, 2, 3, or 4; and

p is 0, 1, 2, 3, 4, or 5.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

(A):

(i) R^a is $-L^{R3}-R^3$; and/or;

(ii) L^{R3} is a covalent bond; and/or

(iii) R^3 is hydrogen or optionally substituted C_{1-6} aliphatic;

or (B):

R^a is $-CH_2CH_3$.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) Ring E is a pyrimidine, pyrimidinone, pyridazine, or pyridazinone ring; or Ring E is a pyrimidine ring; and/or;

(ii) q is 0, 1, or 2; and/or;

(iii) each R^{4A} is independently selected from C_{1-6} aliphatic and $-OC_{1-6}$ aliphatic; or each R^{4A} is independently selected from methyl and methoxy.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^6 is hydrogen, deuterium, or optionally substituted C_{1-6} aliphatic; and/or R^7 is hydrogen or deuterium; or

(ii) R^6 and R^7 are each hydrogen; or R^6 and R^7 are each deuterium.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(A):

(i) D^2 is C-L^{D2}-R^9; and/or

(ii) L^{D2} is a covalent bond; and/or;

(iii) R^9 is hydrogen;

or (B):

D^2 is CH;

or (C):

D^2 is N.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

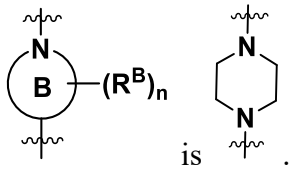
(i) D^3 is CR^{10}; and/or R^{10} is hydrogen or halogen; and/or R^{10} is fluoro; or

(ii) D^3 is CF.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) Ring B is 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or Ring B is 6-membered saturated or partially unsaturated monocyclic heterocyclylene having 1-3 nitrogen atoms; and/or

(ii) n is 0 or 2; or n is 0; or;

(iii)  is .

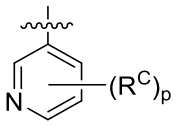
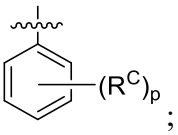
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(A):

(i) Ring C is 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

(ii) Ring C is 6-membered monocyclic heteroaryl having 1-2 nitrogen atoms; or

(iii) Ring C is phenyl; or

(iv) Ring C is  or ;

and/or (B):

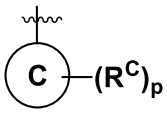
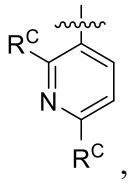
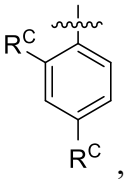
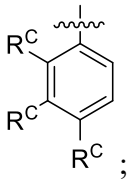
(i) p is 1, 2, or 3; or

(ii) p is 2; or

(iii) p is 3.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(A):

(i)  is selected from , , and ;

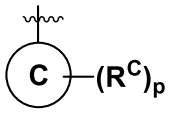
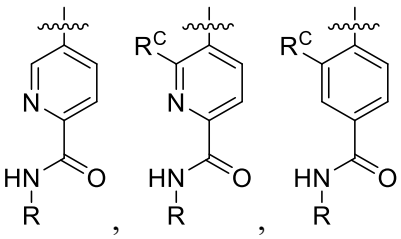
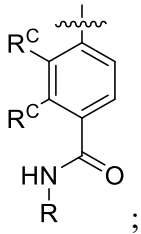
and/or

(ii) each L^{RC} is a covalent bond; and/or;

(iii) each R^{12} is independently selected from halogen, C_{1-6} aliphatic, -C(O)N(R)$_2$, and -C(O)NR(OR); or each R^{12} is independently selected from fluoro, methyl, -C(O)NHR, and -C(O)NH(OR); and/or

(iv) each R is independently selected from hydrogen, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

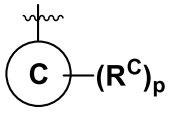
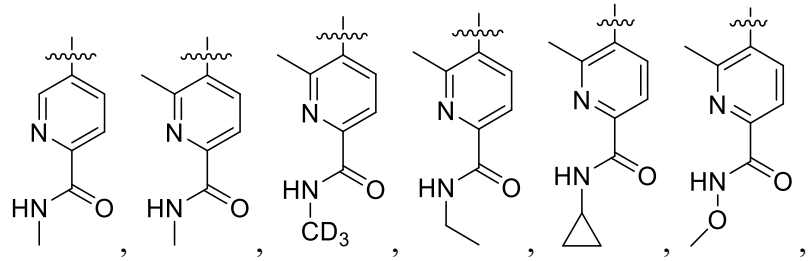
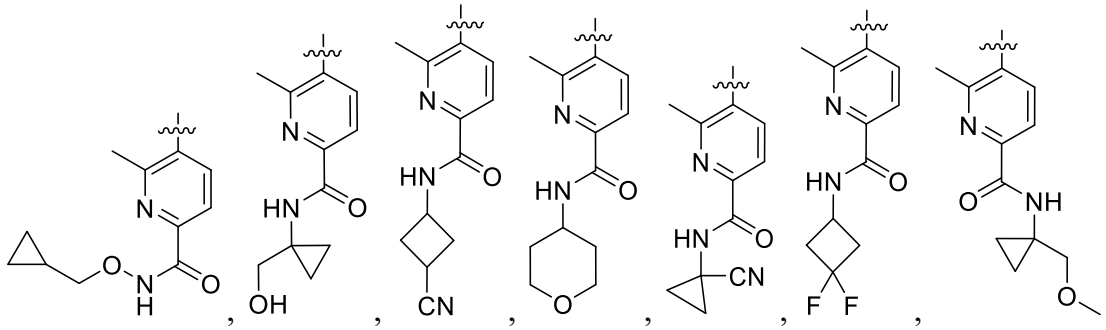
or (B):

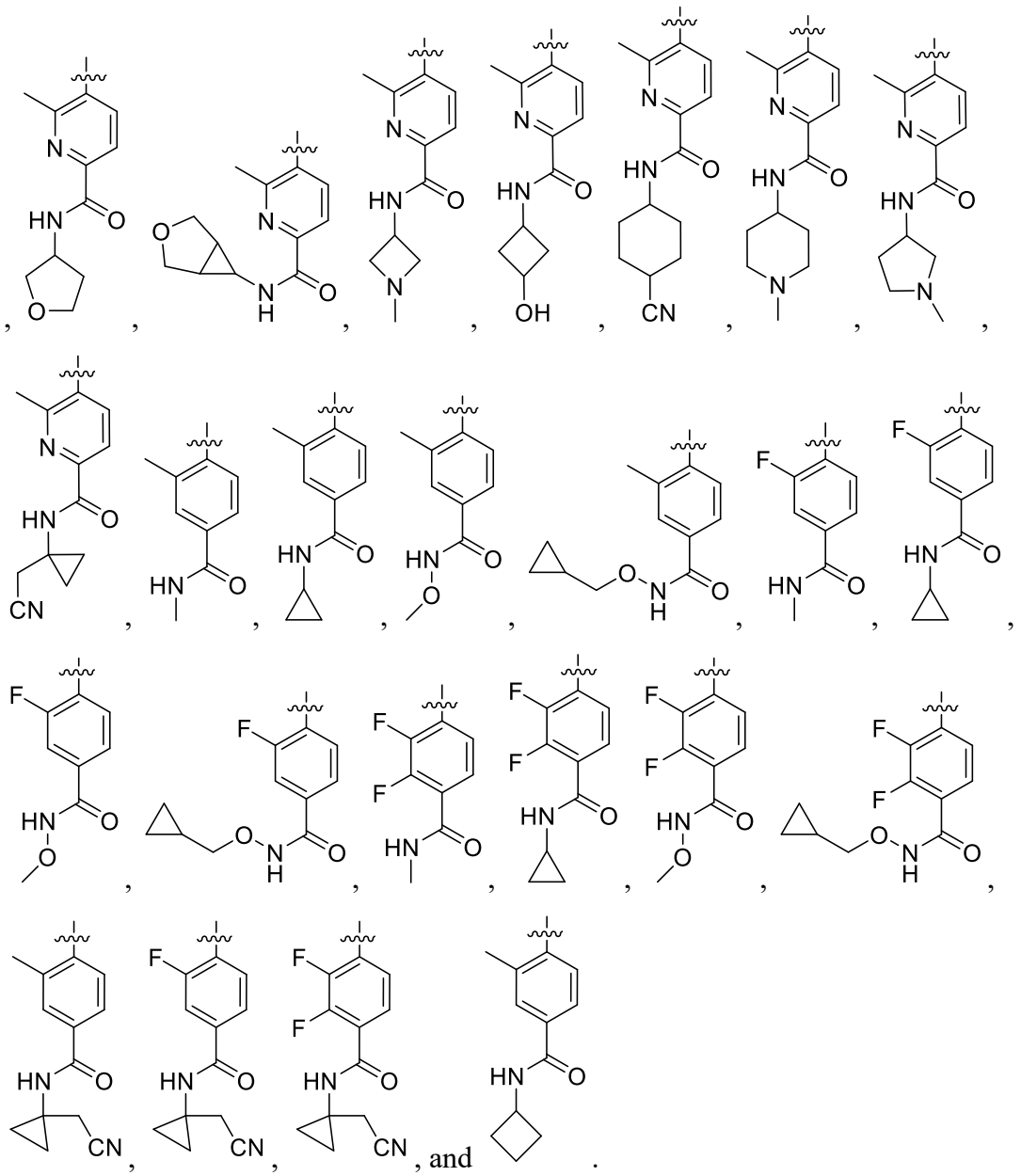
 is selected from , and ;

each R^C is independently selected from methyl and fluoro; and

each R is independently selected from hydrogen, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

or (C):

 is , 



10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R is independently selected from methyl, cyclopropyl, methoxy, cyclopropylmethoxy, cyanocyclopropyl, cyanomethylcyclopropyl, hydroxymethylcyclopropyl, methoxymethylcyclopropyl, cyclobutyl, cyanocyclobutyl, hydroxycyclobutyl, difluorocyclobutyl, cyanocyclohexyl, tetrahydropyranyl, tetrahydrofuranyl, 3-oxabicyclo[3.1.0]hexanyl, methylpyrrolidinyl, and methylpiperidinyl.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(A):

X is $-N(R^a)-$;

R^a is $-L^{R3}-R^3$;

L^{R3} is a covalent bond;

R^3 is hydrogen or optionally substituted C_{1-6} aliphatic;

Ring E is selected from phenyl and 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^{4A} is independently selected from C_{1-6} aliphatic and $-OC_{1-6}$ aliphatic;

D^2 is CH;

D^3 is CR^{10};

R^{10} is hydrogen or halogen;

Ring B is 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each L^{RC} is a covalent bond;

each R^{12} is independently selected from halogen, C_{1-6} aliphatic, $-C(O)N(R)_2$, and -C(O)NR(OR);

each R is independently selected from hydrogen, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0 or 2;

p is 1, 2, or 3; and

q is 0, 1, or 2;

or (B):

X is $-N(R^a)-$;

R^a is $-L^{R3}-R^3$;

L^{R3} is a covalent bond;

R^3 is hydrogen or optionally substituted C_{1-6} aliphatic;

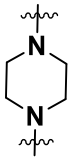
Ring E is a pyrimidine, pyrimidinone, pyridazine, or pyridazinone ring;

each R^{4A} is independently selected from C_{1-6} aliphatic and $-OC_{1-6}$ aliphatic;

D^2 is CH;

D^3 is CR^{10};

R^{10} is hydrogen or halogen;

Ring B is 

;

Ring C is phenyl or 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each L^{RC} is a covalent bond;

each R^{12} is independently selected from halogen, C_{1-6} aliphatic, $-C(O)N(R)_2$, and -C(O)NR(OR);

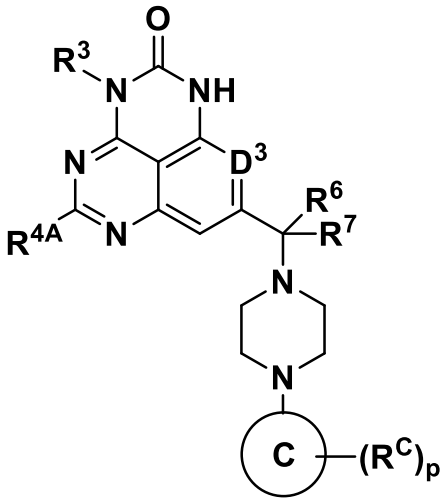
each R is independently selected from hydrogen, C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0;

p is 1, 2, or 3; and

q is 0, 1, or 2.

12. The compound of claim 1, wherein the compound is of Formula IX-a:



IX-a

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, wherein the compound is selected from:

5-(4-((3-ethyl-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

5-(4-((3-ethyl-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((3-ethyl-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N-methyl-6-(trifluoromethyl)picolinamide;

5-(4-((3-ethyl-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide;

5-(4-((3-ethyl-6-fluoro-1-methyl-4-oxo-1,3,4,5-tetrahydropyrazolo[3,4,5-de]quinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-[4-[(12-ethyl-11-oxo-2,3,10,12-tetrazatricyclo[7.3.1.05,13]trideca-1,3,5,7,9(13)-pentaen-7-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamid;

5-(4-((3-ethyl-9-fluoro-5-methoxy-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((3-ethyl-9-fluoro-6-methyl-2,5-dioxo-2,3,5,6-tetrahydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((3-ethyl-9-fluoro-5-methyl-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl-d2)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((9-ethyl-6-fluoro-3-methyl-8-oxo-8,9-dihydro-7H-pyridazino[3,4,5-de]quinazolin-5-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

N-cyclopropyl-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

N-cyclopropyl-5-(4-((9-ethyl-6-fluoro-3-methyl-8-oxo-8,9-dihydro-7H-pyridazino[3,4,5-de]quinazolin-5-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N-methoxy-6-methylpicolinamide;

N-(cyclopropylmethoxy)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N-(1-(hydroxymethyl)cyclopropyl)-6-methylpicolinamide;

N-((1r,3r)-3-cyanocyclobutyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(tetrahydro-2H-pyran-4-yl)picolinamide;

N-(1-cyanocyclopropyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

(S)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(tetrahydro-2H-pyran-3-yl)picolinamide;

N-(3,3-difluorocyclobutyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

N-((1s,3s)-3-cyanocyclobutyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N-(1-(methoxymethyl)cyclopropyl)-6-methylpicolinamide;

(R)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(tetrahydrofuran-3-yl)picolinamide;

(R)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(tetrahydro-2H-pyran-3-yl)picolinamide;

N-((1R,5S,6s)-3-oxabicyclo[3.1.0]hexan-6-yl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

N-((1R,5S,6r)-3-oxabicyclo[3.1.0]hexan-6-yl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(1-methylazetidin-3-yl)picolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N-((1s,3s)-3-hydroxycyclobutyl)-6-methylpicolinamide;

(S)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(tetrahydrofuran-3-yl)picolinamide;

N-((1s,4s)-4-cyanocyclohexyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

N-((1r,4r)-4-cyanocyclohexyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(1-methylpiperidin-4-yl)picolinamide;

(R)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(1-methylpyrrolidin-3-yl)picolinamide;

(S)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methyl-N-(1-methylpyrrolidin-3-yl)picolinamide;

N-(1-(cyanomethyl)cyclopropyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

N-cyclopropyl-5-(4-((9-ethyl-6-fluoro-2-methyl-3,8-dioxo-2,7,8,9-tetrahydro-3H-pyridazino[3,4,5-de]quinazolin-5-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

4-[4-[(6-ethyl-10-fluoro-7-oxo-2,4,6,8-tetrazatricyclo[7.3.1.05,13]trideca-1,3,5(13),9,11-pentaen-11-yl)methyl]piperazin-1-yl]-N,3-dimethyl-benzamide;

N-cyclopropyl-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-methylbenzamide;

4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-N-methoxy-3-methylbenzamide;

N-(cyclopropylmethoxy)-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-methylbenzamide;

4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-fluoro-N-methylbenzamide;

N-cyclopropyl-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-fluorobenzamide;

4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-fluoro-N-methoxybenzamide;

N-(cyclopropylmethoxy)-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-fluorobenzamide;

4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-2,3-difluoro-N-methylbenzamide;

N-cyclopropyl-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-2,3-difluorobenzamide;

4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-2,3-difluoro-N-methoxybenzamide;

N-(cyclopropylmethoxy)-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-2,3-difluorobenzamide;

N-(1-(cyanomethyl)cyclopropyl)-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-methylbenzamide;

N-(1-(cyanomethyl)cyclopropyl)-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-3-fluorobenzamide;

N-(1-(cyanomethyl)cyclopropyl)-4-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-2,3-difluorobenzamide; and

N-cyclobutyl-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide;

or a pharmaceutically acceptable salt thereof.

14. A compound, which is N-cyclopropyl-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide, or a pharmaceutically acceptable salt thereof.

15. A compound, which is N-(1-cyanocyclopropyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide, or a pharmaceutically acceptable salt thereof.

16. A compound, which is N-cyclopropyl-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide.

17. A compound, which is N-(1-cyanocyclopropyl)-5-(4-((3-ethyl-9-fluoro-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]quinazolin-8-yl)methyl)piperazin-1-yl)-6-methylpicolinamide.

18. A pharmaceutical composition comprising a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or a compound of claim 16 or 17, and a pharmaceutically acceptable carrier.

19. Use of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or a compound of claim 16 or 17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for the treatment of a disease, disorder, or condition associated with PARP1.

20. Use of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or a compound of claim 16 or 17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for the treatment of cancer.

21. The use of claim 20, wherein the cancer is selected from breast cancer, ovarian cancer, cervical cancer, epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, endometrial cancer, prostate cancer, testicular cancer, pancreatic cancer, esophageal cancer, head and neck cancer, gastric cancer, bladder cancer, lung cancer, bone cancer, colon cancer, rectal cancer, thyroid cancer, brain and central nervous system cancers, glioblastoma, neuroblastoma, neuroendocrine cancer, rhabdoid cancer, keratoacanthoma, epidermoid carcinoma, seminoma, melanoma, sarcoma, bladder cancer, uterine serous carcinoma, liver cancer, kidney cancer, a myeloid disorder, and a lymphoid disorder.

22. The use of claim 20, wherein the cancer is pancreatic cancer.