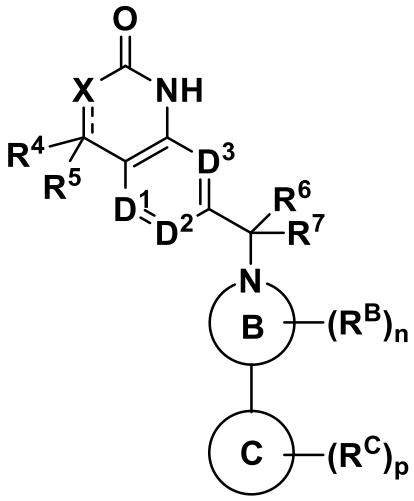
WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

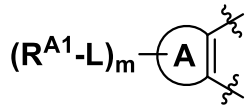
or a pharmaceutically acceptable salt thereof, wherein:

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

X is –C(R^1)=, -C(R^1R^2)-, or -N(R^a)-, as valency allows;

when X is -C(R^1)=, then one of (i)-(iii) applies:

(i) R^5 is absent;

R^1 and R^4 are taken together with the carbon atoms to which they are attached to form  fused to the depicted lactam ring, wherein

Ring A is 5-membered partially unsaturated monocyclic carbocyclyl or 5-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

(ii) R^5 is absent;

R^4 and L^{D1}-R^8 are taken together with the carbon atoms to which they are attached to form an optionally substituted ring selected from 5- to 7-membered partially unsaturated carbocyclyl or 5- to 7-membered partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

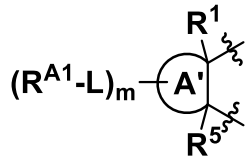
(iii) R^5 is absent;

D^1 is S or NR, and D^2 is absent;

when X is -C(R^1R^2)- or -N(R^a)-:

R^1 and R^2 are each independently 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, -$NRC(O)N(R)_2$, -$NRS(O)N(R)_2$, -$NRS(O)R'$, -$NRS(O)_2N(R)_2$, -$S(O)N(R)_2$, or an optionally substituted group selected from 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; or

R^1 and R^2 are taken together with the carbon atom to which they are attached to form an optionally substituted ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-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 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^2 and R^4 are taken together with the carbon atoms to which they are attached to form  fused to the depicted lactam ring, wherein

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

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

L^{R3} is a covalent bond or optionally substituted bivalent C_{1-6} aliphatic;

R^3 is hydrogen or an optionally substituted group 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;

R^4 and R^5 are each independently 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, $-NRC(O)N(R)_2$, $-NRS(O)N(R)_2$, $-NRS(O)R'$, $-NRS(O)_2N(R)_2$, $-S(O)N(R)_2$, or an optionally substituted group selected from 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; or

R^4 and R^5 are taken together with the carbon atom *C to which they are attached to form *C=O, *C=S, $*C=NR^L$, or an optionally substituted ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-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 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^5 is absent; R^4 and L^{D1}-R^8 are taken together with the carbon to which they are attached to form an optionally substituted ring selected from phenyl, 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^L is hydrogen, -CN, $-OR^{L1}$, or optionally substituted C_{1-6} alkyl;

R^{L1} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

each L is independently a covalent bond or optionally substituted bivalent C_{1-6} aliphatic;

each R^{A1} is independently halogen, -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, $-NRC(O)N(R)_2$, $-C(=NR^m)R'$, $-C(=NR^m)N(R)_2$, $-NRC(=NR^m)N(R)_2$, $-NRC(=NR^m)R'$, $-NRS(O)N(R)_2$, $-NRS(O)R'$, $-NRS(O)(=NR^m)R'$, $-NRS(O)_2N(R)_2$, $-S(O)N(R)_2$, $-OS(O)(=R^m)R'$, $-S(O)(=NR^m)R'$, $-P(O)(R)_2$, or an optionally substituted group 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;

R^6 and R^7 are each independently hydrogen, halogen, or an optionally substituted group selected from 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; or

R^6 and R^7 are taken together with the carbon to which they are attached to form an optionally substituted ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-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 10-membered saturated or partially unsaturated bicyclic

heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

D^1 is C-L^{D1}-R^8, N, NR, or S;

D^2 is absent, C-L^{D2}-R^9, or N, wherein when D^1 is S or NR, D^2 is absent;

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

L^{D1} is a covalent bond or optionally substituted bivalent C_{1-6} aliphatic;

L^{D2} is a covalent bond or optionally substituted bivalent C_{1-6} aliphatic;

R^8 is hydrogen, halogen, -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', $-NRS(O)(=NR^m)R'$, $-NRS(O)_2N(R)_2$, $-S(O)N(R)_2$, $-OS(O)(=R^m)R'$, $-S(O)(=NR^m)R'$, $-P(O)(R)_2$, or an optionally substituted group 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;

R^9 and R^{10} are each independently 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', $-NRS(O)_2N(R)_2$, $-S(O)N(R)_2$, or an optionally substituted group selected from 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;

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 optionally substituted bivalent C_{1-6} aliphatic;

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

each L^{RC} is independently a covalent bond or optionally substituted bivalent C_{1-6} aliphatic;

R^{11} and R^{12} are each independently 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', $-NRS(O)(=NR^m)R'$, $-NRS(O)_2N(R)_2$, $-S(O)N(R)_2$, $-OS(O)(=R^m)R'$, $-S(O)(=NR^m)R'$, $-P(O)(R)_2$, or an optionally substituted group 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; 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 an optionally substituted ring 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;

each R is independently hydrogen or an optionally substituted group 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; or

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

each R’ is independently an optionally substituted group 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; or

two R’ when attached to the same nitrogen atom are taken together to form optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, and sulfur;

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

m is 0, 1, 2, 3, or 4;

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

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

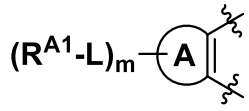
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

⁻⁻⁻⁻⁻ is a single or double bond;

X is $–C(R^1)=$, $-C(R^1R^2)-$, or $-N(R^a)-$, as valency allows;

when X is $-C(R^1)=$, then one of (i)-(iii) applies:

(i) R^5 is absent;

R^1 and R^4 are taken together with the carbon atoms to which they are attached to form  fused to the depicted lactam ring, wherein

Ring A is 5-membered partially unsaturated monocyclic carbocyclyl or 5-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

(ii) R^5 is absent;

R^4 and L^{D1}-R^8 are taken together with the carbon atoms to which they are attached to form a 5- to 7-membered partially unsaturated carbocyclyl or 5- to 7-membered partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the 5- to 7-membered partially unsaturated carbocyclyl or 5- to 7-membered partially unsaturated monocyclic heterocyclyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{4A} substituents; or

(iii) R^5 is absent;

D^1 is S or NR, and D^2 is absent;

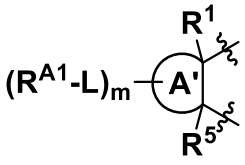
when X is -C(R^1R^2)- or -N(R^a)-:

R^1 and R^2 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)$_2$N(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^{1A} substituents; or

R^1 and R^2 are taken together with the carbon atom to which they are attached to form a 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, a 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, a 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the 3-

to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, a 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, a 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, , and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents; or

R^2 and R^4 are taken together with the carbon atoms to which they are attached



to form fused to the depicted lactam ring, wherein

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

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;

R^4 and R^5 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^{4A} substituents; or

R^4 and R^5 are taken together with the carbon atom *C to which they are attached to form *C=O, *C=S, $*C=NR^L$, a 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, a 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, a 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 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, wherein the 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents; or

R^5 is absent, and R^4 and L^{D1}-R^8, taken together with the carbon to which they are attached, form a group selected from phenyl and 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and

sulfur, wherein the phenyl and 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents;

R^L is hydrogen, -CN, -OR^{L1}, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1, 2, 3, or 4 independently selected R^N substituents;

R^{L1} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

each L 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^{A1} is independently selected from halogen, -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', -$N(R)SO_2$R', -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^{B1} substituents;

R^6 and R^7 are each independently hydrogen, halogen, 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^{6A} substituents; or

R^6 and R^7 are taken together with the carbon to which they are attached to form a 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, a 6- to 10-membered saturated or partially unsaturated bicyclic carbocyclyl, a 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl 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 10-membered saturated or partially unsaturated bicyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{6A} substituents;

D^1 is C-L^{D1}-R^8, N, NR, or S;

D^2 is absent, C-L^{D2}-R^9, or N, wherein when D^1 is S or NR, D^2 is absent;

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

L^{D1} 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;

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^8 is selected from hydrogen, halogen, -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^{8A} 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^{1A}, R^{3A}, R^{4A}, R^{6A}, R^{8A}, R^{9A}, R^{11A}, R^{B1}, 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;

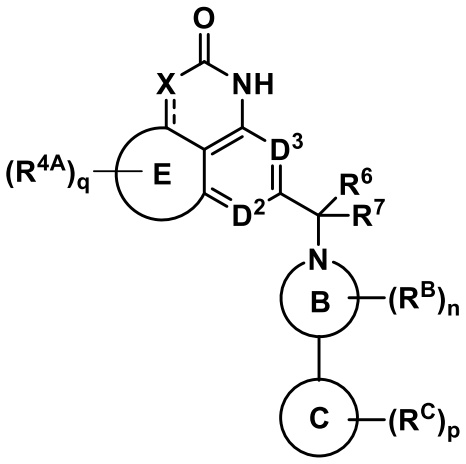
each R^m is independently –OH, -CN, or R;

m is 0, 1, 2, 3, or 4;

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

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

3. The compound of claim 1 or 2, wherein the compound is of Formula VIII:



VIII

or a pharmaceutically acceptable salt thereof, wherein:

when X is -C(R^1)=, Ring E is selected from 5- to 7-membered partially unsaturated carbocyclyl and 5- to 7-membered partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

when X is -C(R^1R^2)- or -N(R^a)-, 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;

each R^{4A} 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–$N(R°)_2$; and

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.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein X is -$N(R^a)$-.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^a is -L^{R3}-R^3.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein L^{R3} is a covalent bond.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or optionally substituted C_{1-6} aliphatic.

8. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^a is $-CH_2CH_3$.

9. The compound of any one of claims 3 to 8, or a pharmaceutically acceptable salt thereof, wherein Ring E is a pyrimidine, pyrimidinone, pyridazine, or pyridazinone ring.

10. The compound of any one of claims 3 to 8, or a pharmaceutically acceptable salt thereof, wherein Ring E is a pyrimidine ring.

11. The compound of any one of claims 3 to 10, or a pharmaceutically acceptable salt thereof, wherein q is 0, 1, or 2.

12. The compound of any one of claims 2 to 11, or a pharmaceutically acceptable salt thereof, wherein each R^{4A} is independently selected from C_{1-6} aliphatic and $-OC_{1-6}$ aliphatic.

13. The compound of any one of claims 2 to 11, or a pharmaceutically acceptable salt thereof, wherein each R^{4A} is independently selected from methyl and methoxy.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen, deuterium, or optionally substituted C_{1-6} aliphatic.

15. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen or deuterium.

16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, deuterium, or optionally substituted C_{1-6} aliphatic.

17. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen or deuterium.

18. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are each hydrogen.

19. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are each deuterium.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein D^2 is $C\text{-}L^{D2}\text{-}R^9$.

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein L^{D2} is a covalent bond.

22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R^9 is hydrogen.

23. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein D^2 is CH.

24. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein D^2 is N.

25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein D^3 is CR^{10}.

26. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^{10} is hydrogen or halogen.

27. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^{10} is fluoro.

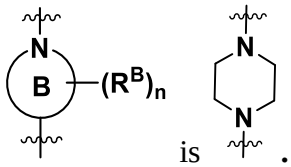
28. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein D^3 is CF.

29. The compound of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein Ring B is 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

30. The compound of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein Ring B is 6-membered saturated or partially unsaturated monocyclic heterocyclylene having 1-3 nitrogen atoms.

31. The compound of any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein n is 0 or 2.

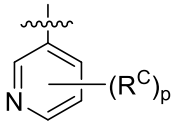
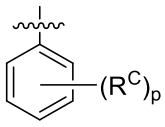
32. The compound of any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein n is 0.

33. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein  is .

34. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein Ring C is 5- to 6-membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

35. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein Ring C is 6-membered monocyclic heteroaryl having 1-2 nitrogen atoms.

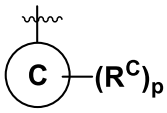
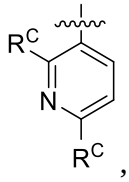
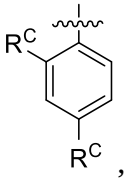
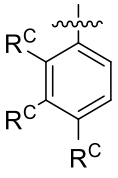
36. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein Ring C is phenyl.

37. The compound of claim 1 to 33, or a pharmaceutically acceptable salt thereof, wherein Ring C is  or .

38. The compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein p is 1, 2, or 3.

39. The compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein p is 2.

40. The compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein p is 3.

41. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein  is selected from , , and .

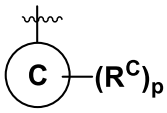
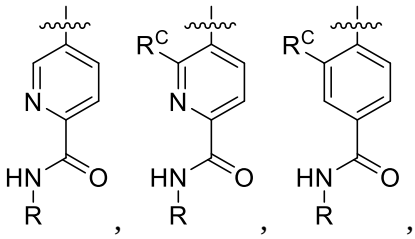
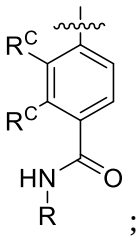
42. The compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, wherein each L^{RC} is a covalent bond.

43. The compound of any one of claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein each R^{12} is independently selected from halogen, C_{1-6} aliphatic, -C(O)N(R)$_2$, and -C(O)NR(OR).

44. The compound of any one of claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein each R^{12} is independently selected from fluoro, methyl, -C(O)NHR, and -C(O)NH(OR).

45. The compound of any one of claims 1 to 44, or a pharmaceutically acceptable salt thereof, wherein each R is independently selected from hydrogen, C_{1-6} aliphatic, 3-

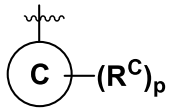
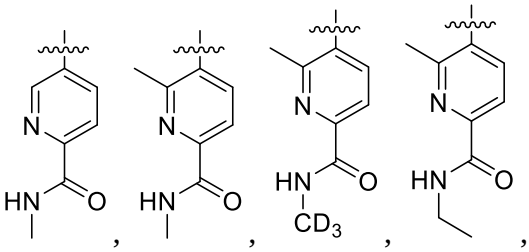
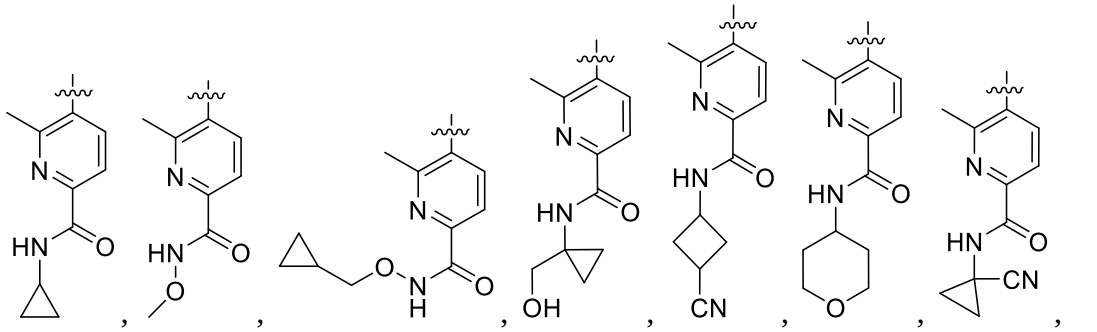
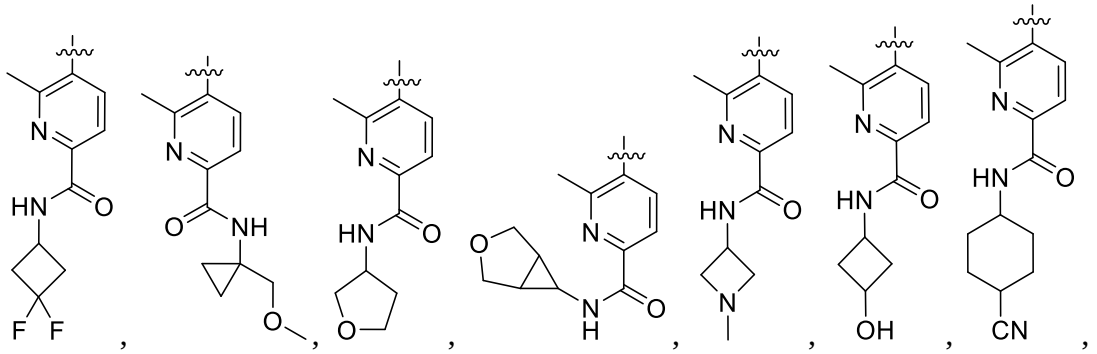
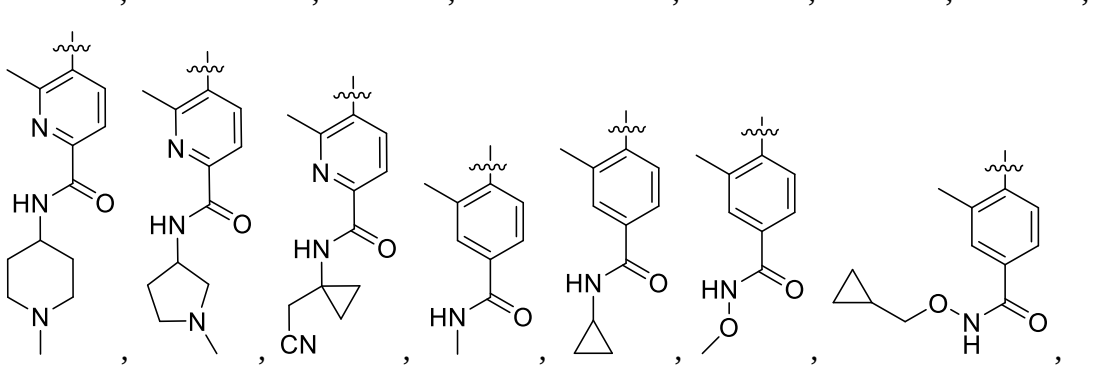
to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

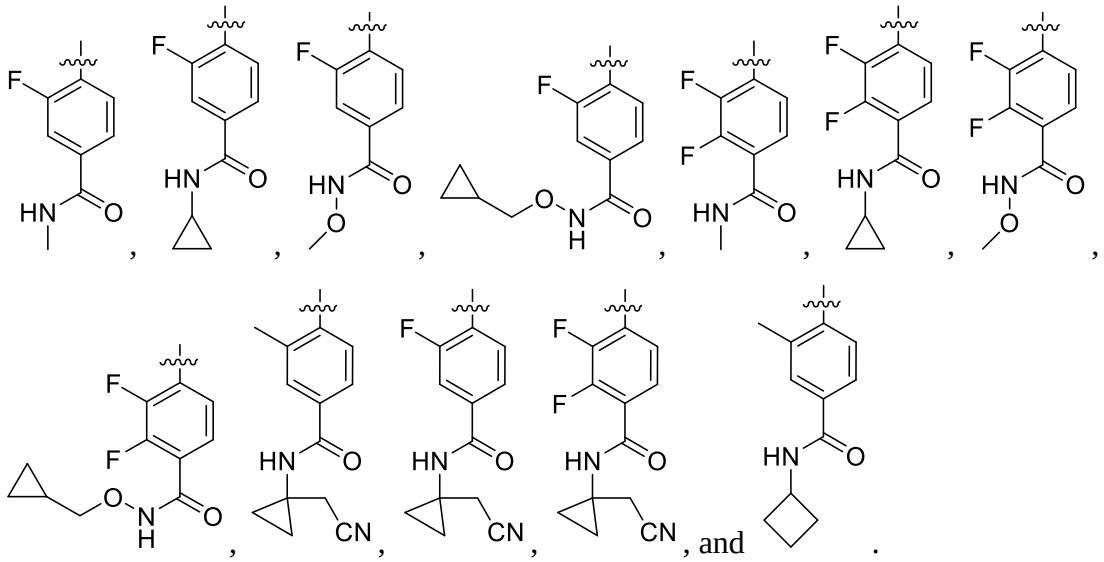
46. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein  is selected from , ;

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.

47. The compound of any one of claims 1 to 46, 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.

48. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein,  is , , , .



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

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;

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

R^7 is hydrogen, deuterium, or optionally substituted C_{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.

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

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;

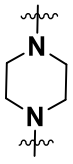
R^6 is hydrogen, deuterium, or optionally substituted C_{1-6} aliphatic;

R^7 is hydrogen, deuterium, or optionally substituted C_{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-

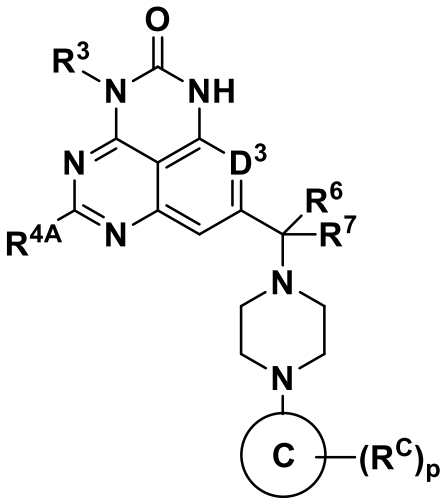
membered saturated or partially unsaturated monocyclic heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0;

p is 1, 2, or 3; and

q is 0, 1, or 2.

51. The compound of any one of claims 1 to 50, wherein the compound is of Formula IX-a:



IX-a

or a pharmaceutically acceptable salt thereof.

52. The compound of claim 1 or 2, wherein the compound is selected from:

5-(4-((3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

5-(4-((3-ethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

N-methyl-5-(4-((2-oxo-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[c]quinolin-5-yl)methyl)piperazin-1-yl)picolinamide;

N-methyl-5-(4-((4-oxo-2,3,4,5-tetrahydro-1H-cyclopenta[c]quinolin-7-yl)methyl)piperazin-1-yl)picolinamide;

N-methyl-5-(4-((2'-oxo-1',4'-dihydro-2'H-spiro[cyclopropane-1,3'-quinolin]-7'-yl)methyl)piperazin-1-yl)picolinamide;

N-methyl-5-(4-((6-oxo-6,7,8,9-tetrahydro-5H-cyclopenta[c][1,5]naphthyridin-3-yl)methyl)piperazin-1-yl)picolinamide;

N-methyl-5-(4-((3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[2,3-c]quinolin-7-yl)methyl)piperazin-1-yl)picolinamide;

N-methyl-5-(4-((1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-7-yl)methyl)piperazin-1-yl)picolinamide;

5-(4-((3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

N-methyl-5-(4-((3-methyl-4-oxo-4,5-dihydro-3H-pyrazolo[3,4-c]quinolin-7-yl)methyl)piperazin-1-yl)picolinamide;

5-(4-((3-ethyl-2-oxo-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-7-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

5-(4-((3-(2,2-difluoroethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

5-(4-((6-ethyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridin-2-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

5-(4-((4-ethyl-5-oxo-2,3,5,6-tetrahydropyrano[4,3,2-de]quinolin-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-methylpicolinamide;

5-(4-((3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-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,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;

N,6-dimethyl-5-(4-((6-oxo-6,7,8,9-tetrahydro-5H-cyclopenta[c][1,5]naphthyridin-3-yl)methyl)piperazin-1-yl)picolinamide;

5-(4-((3-ethyl-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((3-ethyl-5-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

N-methyl-5-(4-((6-oxo-6,7,8,9-tetrahydro-5H-cyclopenta[c][1,5]naphthyridin-3-yl)methyl)piperazin-1-yl)-6-(trifluoromethyl)picolinamide;

6-fluoro-N-methyl-5-(4-((6-oxo-6,7,8,9-tetrahydro-5H-cyclopenta[c][1,5]naphthyridin-3-yl)methyl)piperazin-1-yl)picolinamide;

5-(4-((4-fluoro-6-oxo-6,7,8,9-tetrahydro-5H-cyclopenta[c][1,6]naphthyridin-3-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((4-fluoro-6-oxo-6,7,8,9-tetrahydro-5*H*-cyclopenta[c][1,6]naphthyridin-3-yl)methyl)piperazin-1-yl)-*N*-methylpicolinamide;

6-fluoro-5-(4-((4-fluoro-6-oxo-6,7,8,9-tetrahydro-5*H*-cyclopenta[c][1,6]naphthyridin-3-yl)methyl)piperazin-1-yl)-N-methylpicolinamide;

5-(4-((4-fluoro-6-oxo-6,7,8,9-tetrahydro-5H-cyclopenta[c][1,6]naphthyridin-3-yl)methyl)piperazin-1-yl)-N-methyl-6-(trifluoromethyl)picolinamide;

5-(4-((3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide;

N,6-dimethyl-5-(4-((6-oxo-6,7,8,9-tetrahydro-5H-cyclopenta[c][1,6]naphthyridin-3-yl)methyl)piperazin-1-yl)picolinamide;

5-(4-((3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N-methyl-6-(trifluoromethyl)picolinamide;

5-(4-((5-chloro-3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide; and

5-(4-((3-ethyl-5-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide;

or a pharmaceutically acceptable salt thereof.

53. The compound of claim 1 or 2, wherein the compound is selected from:

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-((3-ethyl-5-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-bis(methyl-d3)picolinamide;

5-(4-((5-(difluoromethyl)-3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((8-fluoro-5-methoxy-3-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((5-chloro-3-ethyl-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((5-cyclopropyl-3-ethyl-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((3-ethyl-8-fluoro-5-(hydroxymethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((5-(cyanomethyl)-3-ethyl-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((5-chloro-3-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N-ethyl-6-methylpicolinamide;

5-(4-((3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-bis(methyl-d3)picolinamide;

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-8-fluoro-5-(methoxymethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((5-(difluoromethyl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

5-(4-((5-chloro-3-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N-ethyl-6-methylpicolinamide; and

5-(4-((5-cyclopropyl-8-fluoro-3-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide;

or a pharmaceutically acceptable salt thereof.

54. The compound of any one of claims 1 to 3 and 51, wherein the compound is selected from:

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.

55. A pharmaceutical composition comprising a compound of any one of claims 1 to 54, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

56. Use of a compound of any one of claims 1 to 54, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 55, in the manufacture of a medicament for inhibition of PARP1.

57. Use of a compound of any one of claims 1 to 54, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 55, in the manufacture of a medicament for the treatment of a disease, disorder, or condition associated with PARP1.

58. Use of a compound of any one of claims 1 to 54, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 55, in the manufacture of a medicament for the treatment of cancer.