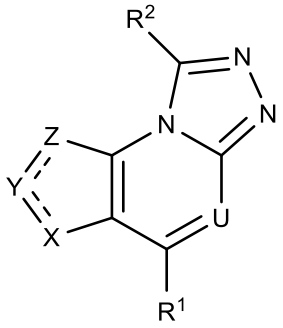
WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

each ⎓ is a single or double bond, wherein at least one ⎓ is a double bond;

U is CR^3 or N;

X is CR^4, N, NR^4, S, or O;

Y is CR^5, N, or NR^5;

Z is CR^6, N, NR^6, S, or O;

R^1 is Cy^1 or L-Cy^1;

L is NR^{c7}, O, C_{1-3} alkyl, C_{2-3} alkenyl, or C_{2-3} alkynyl;

Cy^1 is a C_{3-10} cycloalkyl, 5-15 membered heteroaryl, or 4-15 membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl, 5-15 membered heteroaryl or 4-15 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1A} substituents;

each R^{1A} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a11}, SR^{a11}, $NHOR^{a11}$, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)NR^{c11}(OR^{a11})$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $C(=NR^{e11})R^{b11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $C(=NOR^{a11})R^{b11}$, $C(=NOR^{a11})OR^{a11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})R^{b11}$, $NR^{c11}S(O)R^{b11}$, $NR^{c11}S(O)NR^{c11}R^{d11}$, $NR^{c11}S(O)_2R^{b11}$, $NR^{c11}S(O)(=NR^{e11})R^{b11}$, $NR^{c11}S(O)_2NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$, $OS(O)(=NR^{e11})R^{b11}$, and $OS(O)_2R^{b11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of

R^{1A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1B} substituents;

each R^{a11}, R^{c11}, and R^{d11} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a11}, R^{c11} and R^{d11} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1B} substituents;

or, any R^{c11} and R^{d11} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1B} substituents;

each R^{b11} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b11} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1B} substituents;

each R^{e11} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

each R^{1B} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a12}, SR^{a12}, $NHOR^{a12}$, $C(O)R^{b12}$, $C(O)NR^{c12}R^{d12}$, $C(O)NR^{c12}(OR^{a12})$, $C(O)OR^{a12}$, $OC(O)R^{b12}$, $OC(O)NR^{c12}R^{d12}$, $NR^{c12}R^{d12}$, $NR^{c12}NR^{c12}R^{d12}$, $NR^{c12}C(O)R^{b12}$, $NR^{c12}C(O)OR^{a12}$, $NR^{c12}C(O)NR^{c12}R^{d12}$, $C(=NR^{e12})R^{b12}$, $C(=NR^{e12})NR^{c12}R^{d12}$, $C(=NOR^{a12})R^{b12}$,

$C(=NOR^{a12})OR^{a12}$, $NR^{c12}C(=NR^{e12})NR^{c12}R^{d12}$, $NR^{c12}C(=NR^{e12})R^{b12}$, $NR^{c12}S(O)R^{b12}$, $NR^{c12}S(O)NR^{c12}R^{d12}$, $NR^{c12}S(O)_2R^{b12}$, $NR^{c12}S(O)(=NR^{e12})R^{b12}$, $NR^{c12}S(O)_2NR^{c12}R^{d12}$, $S(O)R^{b12}$, $S(O)NR^{c12}R^{d12}$, $S(O)_2R^{b12}$, $S(O)_2NR^{c12}R^{d12}$, $OS(O)(=NR^{e12})R^{b12}$, and $OS(O)_2R^{b12}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1C} substituents;

each R^{a12}, R^{c12}, and R^{d12} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a12}, R^{c12} and R^{d12} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1C} substituents;

or, any R^{c12} and R^{d12} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1C} substituents;

each R^{b12} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b12} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{1C} substituents;

each R^{e12} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

each R^{1C} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a13}, SR^{a13}, $NHOR^{a13}$, $C(O)R^{b13}$, $C(O)NR^{c13}R^{d13}$, $C(O)NR^{c13}(OR^{a13})$, $C(O)OR^{a13}$, $OC(O)R^{b13}$, $OC(O)NR^{c13}R^{d13}$, $NR^{c13}R^{d13}$, $NR^{c13}NR^{c13}R^{d13}$, $NR^{c13}C(O)R^{b13}$, $NR^{c13}C(O)OR^{a13}$, $NR^{c13}C(O)NR^{c13}R^{d13}$, $C(=NR^{e13})R^{b13}$, $C(=NR^{e13})NR^{c13}R^{d13}$, $C(=NOR^{a12})R^{b12}$, $C(=NOR^{a12})OR^{a12}$, $NR^{c13}C(=NR^{e13})NR^{c13}R^{d13}$, $NR^{c13}C(=NR^{e13})R^{b13}$, $NR^{c13}S(O)R^{b13}$, $NR^{c13}S(O)NR^{c13}R^{d13}$, $NR^{c13}S(O)_2R^{b13}$, $NR^{c13}S(O)(=NR^{e13})R^{b13}$, $NR^{c13}S(O)_2NR^{c13}R^{d13}$, $S(O)R^{b13}$, $S(O)NR^{c13}R^{d13}$, $S(O)_2R^{b13}$, $S(O)_2NR^{c13}R^{d13}$, $OS(O)(=NR^{e13})R^{b13}$, and $OS(O)_2R^{b13}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1D} substituents;

each R^{a13}, R^{c13}, and R^{d13} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a13}, R^{c13} and R^{d13} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1D} substituents;

or, any R^{c13} and R^{d13} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^{1D} substituents;

each R^{b13} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b13} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1D} substituents;

each R^{e13} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-;

each R^{1D} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a14}, SR^{a14}, $NHOR^{a14}$, $C(O)R^{b14}$, $C(O)NR^{c14}R^{d14}$, $C(O)NR^{c14}(OR^{a14})$, $C(O)OR^{a14}$, $OC(O)R^{b14}$, $OC(O)NR^{c14}R^{d14}$, $NR^{c14}R^{d14}$, $NR^{c14}NR^{c14}R^{d14}$, $NR^{c14}C(O)R^{b14}$, $NR^{c14}C(O)OR^{a14}$, $NR^{c14}C(O)NR^{c14}R^{d14}$, $C(=NR^{e14})R^{b14}$, $C(=NR^{e14})NR^{c14}R^{d14}$, $NR^{c14}C(=NR^{e14})NR^{c14}R^{d14}$, $NR^{c14}C(=NR^{e14})R^{b14}$, $NR^{c14}S(O)R^{b14}$, $NR^{c14}S(O)NR^{c14}R^{d14}$, $NR^{c14}S(O)_2R^{b14}$, $NR^{c14}S(O)(=NR^{e14})R^{b14}$, $NR^{c14}S(O)_2NR^{c14}R^{d14}$, $S(O)R^{b14}$, $S(O)NR^{c14}R^{d14}$, $S(O)_2R^{b14}$, $S(O)_2NR^{c14}R^{d14}$, $OS(O)(=NR^{e14})R^{b14}$, and $OS(O)_2R^{b14}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1D} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a14}, R^{c14}, and R^{d14} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a14}, R^{c14} and R^{d14} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c14} and R^{d14} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{b14} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-

$_6$ alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b14} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e14} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^2 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a2}, $NHOR^{a2}$, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)NR^{c2}(OR^{a2})$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $C(=NR^{e2})R^{b2}$, $C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})R^{b2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)(=NR^{e2})R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, $S(O)_2NR^{c2}R^{d2}$, $OS(O)(=NR^{e2})R^{b2}$, and $OS(O)_2R^{b2}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2A} substituents;

each R^{a2}, R^{c2}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a2}, R^{c2} and R^{d2} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2A} substituents;

or, any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2A} substituents;

each R^{b2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered

heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b2} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2A} substituents;

each R^{e2} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^{2A} is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, and $OS(O)_2R^{b21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a21}, R^{c21}, and R^{d21} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c21} and R^{d21} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl

group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{b21} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e21} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^3 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a3}, SR^{a3}, $NHOR^{a3}$, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)NR^{c3}(OR^{a3})$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $C(=NR^{e3})R^{b3}$, $C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})R^{b3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)(=NR^{e3})R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, $OS(O)(=NR^{e3})R^{b3}$, and $OS(O)_2R^{b3}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^3 are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3A} substituents;

each R^{a3}, R^{c3}, and R^{d3} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a3}, R^{c3} and R^{d3}

are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3A} substituents;

or, any R^{c3} and R^{d3} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3A} substituents;

each R^{b3} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b3} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3A} substituents;

each R^{e3} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^{3A} is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a31}, SR^{a31}, $NHOR^{a31}$, $C(O)R^{b31}$, $C(O)NR^{c31}R^{d31}$, $C(O)NR^{c31}(OR^{a31})$, $C(O)OR^{a31}$, $OC(O)R^{b31}$, $OC(O)NR^{c31}R^{d31}$, $NR^{c31}R^{d31}$, $NR^{c31}NR^{c31}R^{d31}$, $NR^{c31}C(O)R^{b31}$, $NR^{c31}C(O)OR^{a31}$, $NR^{c31}C(O)NR^{c31}R^{d31}$, $C(=NR^{e31})R^{b31}$, $C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})R^{b31}$, $NR^{c31}S(O)R^{b31}$, $NR^{c31}S(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)_2R^{b31}$, $NR^{c31}S(O)(=NR^{e31})R^{b31}$, $NR^{c31}S(O)_2NR^{c31}R^{d31}$, $S(O)R^{b31}$, $S(O)NR^{c31}R^{d31}$, $S(O)_2R^{b31}$, $S(O)_2NR^{c31}R^{d31}$, $OS(O)(=NR^{e31})R^{b31}$, and $OS(O)_2R^{b31}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a31}, R^{c31}, and R^{d31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-

C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a31}, R^{c31} and R^{d31} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c31} and R^{d31} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{b31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b31} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e31} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^4 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a4}, SR^{a4}, $NHOR^{a4}$, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)NR^{c4}(OR^{a4})$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $C(=NR^{e4})R^{b4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})R^{b4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)(=NR^{e4})R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, $OS(O)(=NR^{e4})R^{b4}$, and $OS(O)_2R^{b4}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^4 are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4A} substituents;

each R^{a4}, R^{c4}, and R^{d4} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a4}, R^{c4} and R^{d4} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4A} substituents;

or, any R^{c4} and R^{d4} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4A} substituents;

each R^{b4} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b4} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4A} substituents;

each R^{e4} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^{4A} is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a41}, SR^{a41}, $NHOR^{a41}$, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, $C(O)NR^{c41}(OR^{a41})$, $C(O)OR^{a41}$, $OC(O)R^{b41}$, $OC(O)NR^{c41}R^{d41}$, $NR^{c41}R^{d41}$, $NR^{c41}NR^{c41}R^{d41}$, $NR^{c41}C(O)R^{b41}$, $NR^{c41}C(O)OR^{a41}$, $NR^{c41}C(O)NR^{c41}R^{d41}$, $C(=NR^{e41})R^{b41}$, $C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})R^{b41}$, $NR^{c41}S(O)R^{b41}$, $NR^{c41}S(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)_2R^{b41}$, $NR^{c41}S(O)(=NR^{e41})R^{b41}$, $NR^{c41}S(O)_2NR^{c41}R^{d41}$, $S(O)R^{b41}$, $S(O)NR^{c41}R^{d41}$, $S(O)_2R^{b41}$, $S(O)_2NR^{c41}R^{d41}$, $OS(O)(=NR^{e41})R^{b41}$, and $OS(O)_2R^{b41}$, wherein the C_{1-6} alkyl, C_{2-6}

alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a41}, R^{c41}, and R^{d41} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a41}, R^{c41} and R^{d41} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c41} and R^{d41} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{b41} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b41} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e41} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^5 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a5}, SR^{a5}, $NHOR^{a5}$, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)NR^{c5}(OR^{a5})$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $C(=NR^{e5})R^{b5}$, $C(=NR^{e5})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{e5})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{e5})R^{b5}$, $NR^{c5}S(O)R^{b5}$,

$NR^{c5}S(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)(=NR^{e5})R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, $OS(O)(=NR^{e5})R^{b5}$, and $OS(O)_2R^{b5}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^5 are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{5A} substituents;

each R^{a5}, R^{c5}, and R^{d5} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a5}, R^{c5} and R^{d5} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{5A} substituents;

or, any R^{c5} and R^{d5} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{5A} substituents;

each R^{b5} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b5} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{5A} substituents;

each R^{e5} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^{5A} is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered

heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a51}, SR^{a51}, $NHOR^{a51}$, $C(O)R^{b51}$, $C(O)NR^{c51}R^{d51}$, $C(O)NR^{c51}(OR^{a51})$, $C(O)OR^{a51}$, $OC(O)R^{b51}$, $OC(O)NR^{c51}R^{d51}$, $NR^{c51}R^{d51}$, $NR^{c51}NR^{c51}R^{d51}$, $NR^{c51}C(O)R^{b51}$, $NR^{c51}C(O)OR^{a51}$, $NR^{c51}C(O)NR^{c51}R^{d51}$, $C(=NR^{e51})R^{b51}$, $C(=NR^{e51})NR^{c51}R^{d51}$, $NR^{c51}C(=NR^{e51})NR^{c51}R^{d51}$, $NR^{c51}C(=NR^{e51})R^{b51}$, $NR^{c51}S(O)R^{b51}$, $NR^{c51}S(O)NR^{c51}R^{d51}$, $NR^{c51}S(O)_2R^{b51}$, $NR^{c51}S(O)(=NR^{e51})R^{b51}$, $NR^{c51}S(O)_2NR^{c51}R^{d51}$, $S(O)R^{b51}$, $S(O)NR^{c51}R^{d51}$, $S(O)_2R^{b51}$, $S(O)_2NR^{c51}R^{d51}$, $OS(O)(=NR^{e51})R^{b51}$, and $OS(O)_2R^{b51}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{5A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a51}, R^{c51}, and R^{d51} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a51}, R^{c51} and R^{d51} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c51} and R^{d51} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{b51} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b51} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e51} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^6 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a6}, SR^{a6}, $NHOR^{a6}$, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)NR^{c6}(OR^{a6})$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $C(=NR^{e6})R^{b6}$, $C(=NR^{e6})NR^{c6}R^{d6}$, $NR^{c6}C(=NR^{e6})NR^{c6}R^{d6}$, $NR^{c6}C(=NR^{e6})R^{b6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)(=NR^{e6})R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, $S(O)_2NR^{c6}R^{d6}$, $OS(O)(=NR^{e6})R^{b6}$, and $OS(O)_2R^{b6}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^6 are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{6A} substituents;

each R^{a6}, R^{c6}, and R^{d6} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a6}, R^{c6} and R^{d6} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{6A} substituents;

or, any R^{c6} and R^{d6} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{6A} substituents;

each R^{b6} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b6} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{6A} substituents;

each R^{e6} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^{6A} is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a61}, SR^{a61}, $NHOR^{a61}$, $C(O)R^{b61}$, $C(O)NR^{c61}R^{d61}$, $C(O)NR^{c61}(OR^{a61})$, $C(O)OR^{a61}$, $OC(O)R^{b61}$, $OC(O)NR^{c61}R^{d61}$, $NR^{c61}R^{d61}$, $NR^{c61}NR^{c61}R^{d61}$, $NR^{c61}C(O)R^{b61}$, $NR^{c61}C(O)OR^{a61}$, $NR^{c61}C(O)NR^{c61}R^{d61}$, $C(=NR^{e61})R^{b61}$, $C(=NR^{e61})NR^{c61}R^{d61}$, $NR^{c61}C(=NR^{e61})NR^{c61}R^{d61}$, $NR^{c61}C(=NR^{e61})R^{b61}$, $NR^{c61}S(O)R^{b61}$, $NR^{c61}S(O)NR^{c61}R^{d61}$, $NR^{c61}S(O)_2R^{b61}$, $NR^{c61}S(O)(=NR^{e61})R^{b61}$, $NR^{c61}S(O)_2NR^{c61}R^{d61}$, $S(O)R^{b61}$, $S(O)NR^{c61}R^{d61}$, $S(O)_2R^{b61}$, $S(O)_2NR^{c61}R^{d61}$, $OS(O)(=NR^{e61})R^{b61}$, and $OS(O)_2R^{b61}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{6A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a61}, R^{c61}, and R^{d61} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a61}, R^{c61} and R^{d61} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c61} and R^{d61} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{b61} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-}

$_6$ alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b61} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e61} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^{c7} is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{c7} is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{7A} substituents;

each R^{7A} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-15} aryl, C_{3-15} cycloalkyl, 5-15 membered heteroaryl, 4-15 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a71}, SR^{a71}, $NHOR^{a71}$, $C(O)R^{b71}$, $C(O)NR^{c71}R^{d71}$, $C(O)NR^{c71}(OR^{a71})$, $C(O)OR^{a71}$, $OC(O)R^{b71}$, $OC(O)NR^{c71}R^{d71}$, $NR^{c71}R^{d71}$, $NR^{c71}NR^{c71}R^{d71}$, $NR^{c71}C(O)R^{b71}$, $NR^{c71}C(O)OR^{a71}$, $NR^{c71}C(O)NR^{c71}R^{d71}$, $C(=NR^{e71})R^{b71}$, $C(=NR^{e71})NR^{c71}R^{d71}$, $C(=NOR^{a71})R^{b71}$, $C(=NOR^{a71})OR^{a71}$, $NR^{c71}C(=NR^{e71})NR^{c71}R^{d71}$, $NR^{c71}C(=NR^{e71})R^{b71}$, $NR^{c71}S(O)R^{b71}$, $NR^{c71}S(O)NR^{c71}R^{d71}$, $NR^{c71}S(O)_2R^{b71}$, $NR^{c71}S(O)(=NR^{e71})R^{b71}$, $NR^{c71}S(O)_2NR^{c71}R^{d71}$, $S(O)R^{b71}$, $S(O)NR^{c71}R^{d71}$, $S(O)_2R^{b71}$, $S(O)_2NR^{c71}R^{d71}$, $OS(O)(=NR^{e71})R^{b71}$, and $OS(O)_2R^{b71}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{7A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{7B} substituents;

each R^{a71}, R^{c71}, and R^{d71} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10

membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a71}, R^{c71} and R^{d71} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{7B} substituents;

or, any R^{c71} and R^{d71} attached to the same N atom, together with the N atom to which they are attached, form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl group, wherein the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{7B} substituents;

each R^{b71} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b71} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{7B} substituents;

each R^{e71} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-;

each R^{7B} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a72}, SR^{a72}, $NHOR^{a72}$, $C(O)R^{b72}$, $C(O)NR^{c72}R^{d72}$, $C(O)NR^{c72}(OR^{a72})$, $C(O)OR^{a72}$, $OC(O)R^{b72}$, $OC(O)NR^{c72}R^{d72}$, $NR^{c72}R^{d72}$, $NR^{c72}NR^{c72}R^{d72}$, $NR^{c72}C(O)R^{b72}$, $NR^{c72}C(O)OR^{a72}$, $NR^{c72}C(O)NR^{c72}R^{d72}$, $C(=NR^{e72})R^{b72}$, $C(=NR^{e72})NR^{c72}R^{d72}$, $NR^{c72}C(=NR^{e72})NR^{c72}R^{d72}$, $NR^{c72}C(=NR^{e72})R^{b72}$, $NR^{c72}S(O)R^{b72}$, $NR^{c72}S(O)NR^{c72}R^{d72}$, $NR^{c72}S(O)_2R^{b72}$, $NR^{c72}S(O)(=NR^{e72})R^{b72}$, $NR^{c72}S(O)_2NR^{c72}R^{d72}$, $S(O)R^{b72}$, $S(O)NR^{c72}R^{d72}$, $S(O)_2R^{b72}$, $S(O)_2NR^{c72}R^{d72}$, $OS(O)(=NR^{e72})R^{b72}$, and $OS(O)_2R^{b72}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{7B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{M} substituents;

each R^{a72}, R^{c72}, and R^{d72} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{a72}, R^{c72} and R^{d72} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c72} and R^{d72} attached to the same N atom, together with the N atom to which they are attached, form a 5-6 membered heteroaryl or a 4-7 membered heterocycloalkyl group, wherein the 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl group is optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{b72} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{b72} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e72} is independently selected from H, OH, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-; and

each R^M is independently selected from H, OH, halo, oxo, CN, C(O)OH, NH_2, NO_2, SF_5, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein U is CH or N.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^4 is H or C_{1-6} alkyl.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein X is CH, CCH_3, N, $-NCH_2CH_3$, S, or O.

6. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein Y is CR^5 or N.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^5 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{5A} substituents.

8. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl of R^5 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{5A} substituents.

9. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, and 5-6 membered heteroaryl, wherein the C_{1-6} alkyl and 5-6 membered heteroaryl of R^5 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{5A} substituents.

10. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from H, methyl, ethyl, difluoromethyl, and pyrazolyl, wherein

the methyl, ethyl, and pyrazolyl of R^5 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{5A} substituents.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein each R^{5A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and CN.

12. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein each R^{5A} is CN.

13. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from H, methyl, cyanoethyl, difluoromethyl, and pyrazolyl.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Z is CR^6, NR^6, or S.

15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl-C_{1-6} alkyl-, or (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- are each optionally substituted by 1, 2, 3, or 4 independently selected R^{6A} subsitutents.

16. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, C_{1-6} alkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl-, or (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl-, or (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- are each optionally substituted by 1, 2, 3, or 4 independently selected R^{6A} subsitutents.

17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein each R^{6A} is independently selected from $NR^{c61}R^{d61}$, wherein each R^{c61} and R^{d61} is independently selected from H and C_{1-6} alkyl.

18. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, C_{1-6} alkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl-, or (4-7 membered

heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl is optionally substituted by $NR^{c61}R^{d61}$, wherein the R^{c61} and R^{d61} are each independently selected from H and C_{1-6} alkyl.

19. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, methyl, cyclopropylmethyl, tetrahydrofuranylmethyl, and dimethylaminoethyl.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein Z is CH, NCH_3, $NCH_2CH_2N(CH_3)_2$, NCH_2-cyclopropyl, NCH_2-tetrahydrofuranyl, or S.

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^1 is Cy^1.

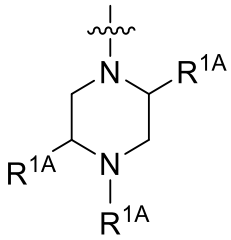
22. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is a C_{3-7} cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents.

23. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is a 4-7 membered heterocycloalkyl which is optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents.

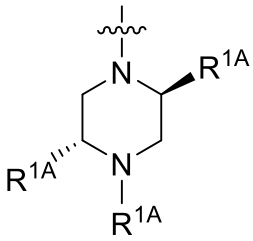
24. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is piperazinyl, which is optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents.

25. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is piperazinyl, which is substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents.

26. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is:



27. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is:



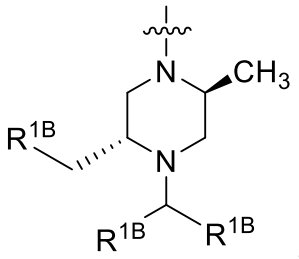
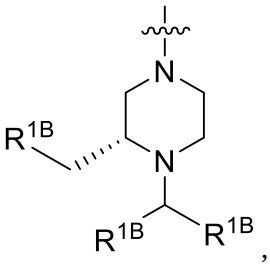
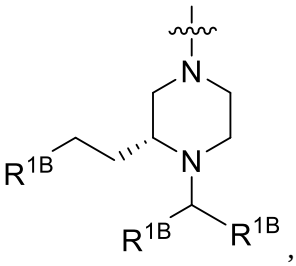
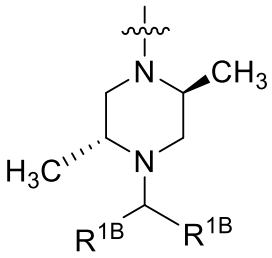
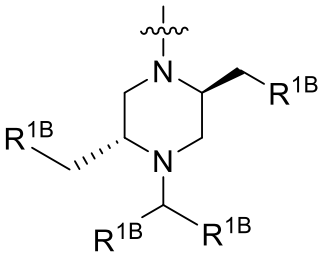
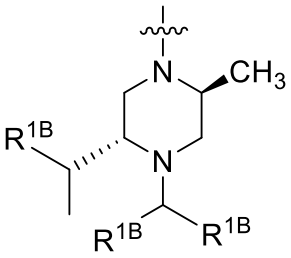
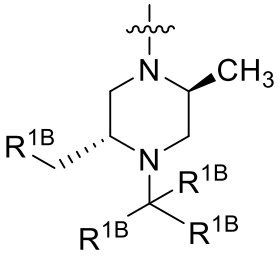
28. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1B} substituents.

29. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{1A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1B} substituents.

30. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl, wherein the C_{1-6} alkyl of R^{1A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1B} substituents.

31. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently selected from C_{1-6} alkyl, each of which are optionally substituted with 1, 2, 3, or 4 independently selected R^{1B} substituents.

32. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is:


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, or

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33. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, and OR^{a12}, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents.

34. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from C_{1-6} alkyl, C_{6-10} aryl, C_{3-10}

cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, and OR^{a12}, wherein the C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents.

35. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, and OR^{a12}, wherein the phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents.

36. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, CN, and OR^{a12}, wherein the C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents.

37. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, CN, and OR^{a12}, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, and 5-6 membered heteroaryl, of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents; and

each R^{a12} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

38. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, pyridinyl, CN, and OR^{a12}, wherein the C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, and pyridinyl of R^{1B}

are each optionally substituted with 1, 2, 3, or 4 R^{1C} substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, and OR^{a13};

each R^{a12} is independently selected from H and C_{1-6} alkyl; and

each R^{a13} is independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl.

39. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from methyl, isopropyl, cyclobutyl, cyclohexyl, phenyl, pyridinyl, CN, and methoxy, wherein each methyl, isopropyl, cyclobutyl, cyclohexyl, phenyl, and pyridinyl of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents.

40. The compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein each R^{1C} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, and OR^{a13}; and

each R^{a13} is independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl.

41. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is independently selected from isopropyl, hydroxymethyl, difluorocyclobutyl, trifluoromethylcyclobutyl, difluorocyclohexyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, bromophenyl, bromofluorophenyl, chlorofluorophenyl, (fluoro)(difluoromethyl)phenyl, (fluoro)(trifluoromethyl)phenyl, (chloro)(methyl)phenyl, difluoromethylphenyl, trifluoromethylphenyl, (trifluoromethyl)(methyl)phenyl, (trifluoromethyl)(difluoro)phenyl, (chloro)(trifluoromethyl)phenyl, (chloro)(difluoro)phenyl, (trifluoromethoxy)(fluoro)phenyl, trifluoromethoxyphenyl, methoxyphenyl, cyanophenyl, trifluoromethylpyridinyl, (trifluoromethyl)(fluoro)pyridinyl, trifluoromethoxypyridinyl, CN, and methoxy.

42. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered

heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents.

43. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents.

44. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein the C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents.

45. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from H, C_{1-6} alkyl, and C_{3-7} cycloalkyl.

46. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from H, methyl, and cyclopropyl.

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

each $\overline{\quad}$ is a single or double bond, wherein at least one $\overline{\quad}$ is a double bond;

U is CH or N;

X is CR^4, N, NR^4, S, or O;

Y is CR^5 or N;

Z is CR^6, NR^6, or S;

R^1 is Cy^1 or L-Cy^1;

L is NR^{c7}, O, C_{1-3} alkyl, C_{2-3} alkenyl, or C_{2-3} alkynyl;

Cy^1 is a C_{3-10} cycloalkyl, 5-15 membered heteroaryl, or 4-15 membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl, 5-15 membered heteroaryl or 4-15 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents;

each R^{1A} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1B} substituents;

each R^{1B} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, and OR^{a12}, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents;

each R^{1C} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, and OR^{a13};

each R^{a13} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^2 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents;

each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-7} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-;

R^4 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^5 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^5 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{5A} substituents;

each R^{5A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and CN;

R^6 is H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl-C_{1-6} alkyl-, or (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- are each optionally substituted by 1, 2, 3, or 4 independently selected R^{6A} subsitutents;

each R^{6A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and $NR^{c61}R^{d61}$;

each R^{c61} and R^{d61} is independently selected from H and C_{1-6} alkyl; and

R^{c7} is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-.

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

U is CH or N;

X is CR^4, N, NR^4, S, or O;

Y is CR^5 or N;

Z is CR^6, NR^6, or S;

R^1 is Cy^1;

Cy^1 is a C_{3-7} cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents;

each R^{1A} is independently selected from halo, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{1A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1B} substituents;

each R^{1B} is independently selected from C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, and OR^{a12}, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, C_{3-10} cycloalkyl-C_{1-6} alkyl-, (5-10 membered heteroaryl)-C_{1-6} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents;

each R^{1C} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and OR^{a13};

each R^{a12} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

each R^{a13} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^2 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents;

R^4 is H or C_{1-6} alkyl;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl of R^5 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{5A} substituents;

each R^{5A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and CN;

R^6 is H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl-C_{1-6} alkyl-, or (4-7 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- are each optionally substituted by $NR^{c61}R^{d61}$; and

each R^{c61} and R^{d61} is independently selected from H and C_{1-6} alkyl.

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

U is CH or N;

X is CH, CCH_3, N, $-NCH_2CH_3$, S, or O;

Y is CR^5 or N;

Z is CH, NCH_3, $NCH_2CH_2N(CH_3)_2$, NCH_2-cyclopropyl, NCH_2-tetrahydrofuranyl, or S;

R^1 is Cy^1;

Cy^1 is a 4-7 membered heterocycloalkyl which is optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents;

each R^{1A} is independently selected from C_{1-6} alkyl, each of which are optionally substituted with 1, 2, 3, or 4 independently selected R^{1B} substituents;

each R^{1B} is independently selected from C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, CN, and OR^{a12}, wherein the C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl of R^{1B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{1C} substituents;

each R^{1C} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and OR^{a13};

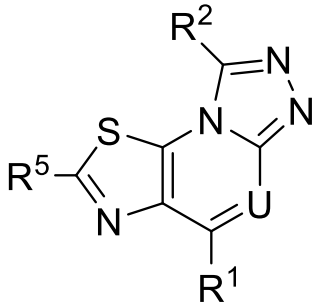
each R^{a12} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

each R^{a13} is independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, and 5-6 membered heteroaryl, wherein the C_{1-6} alkyl and 5-6 membered heteroaryl of R^5 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{5A} substituents; and

each R^{5A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and CN.

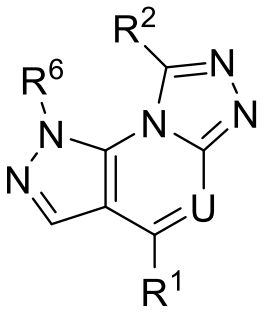
50. The compound of claim 1, wherein the compound of Formula I is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof.

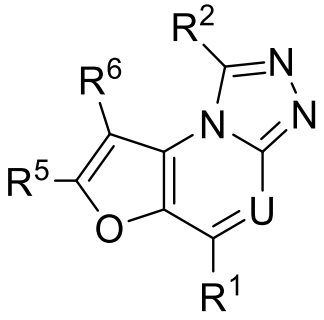
51. The compound of claim 1, wherein the compound of Formula I is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof.

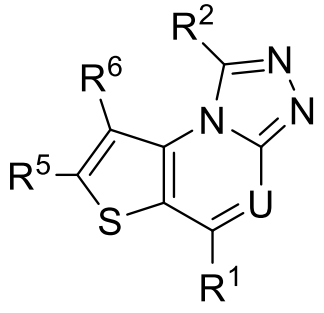
52. The compound of claim 1, wherein the compound of Formula I is a compound of Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

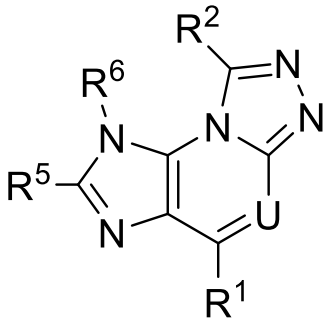
53. The compound of claim 1, wherein the compound of Formula I is a compound of Formula V:



V

or a pharmaceutically acceptable salt thereof.

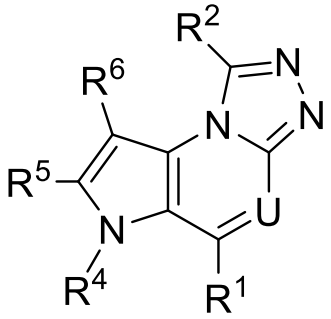
54. The compound of claim 1, wherein the compound of Formula I is a compound of Formula VI:



VI

or a pharmaceutically acceptable salt thereof.

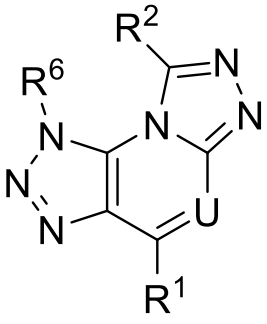
55. The compound of claim 1, wherein the compound of Formula I is a compound of Formula VII:



VII

or a pharmaceutically acceptable salt thereof.

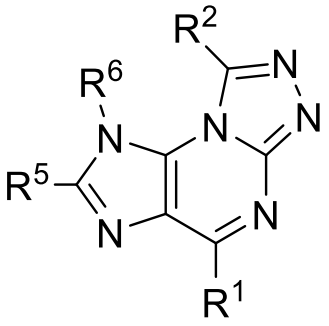
56. The compound of claim 1, wherein the compound of Formula I is a compound of Formula VIII:



VIII

or a pharmaceutically acceptable salt thereof.

57. The compound of claim 1, wherein the compound of Formula I is a compound of Formula IX:



IX

or a pharmaceutically acceptable salt thereof.

58. The compound of claim 1, which is selected from:

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)thiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-8-methylthiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-(difluoromethyl)thiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

3-(4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)thiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-2-yl)propanenitrile;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-(1*H*-pyrazol-4-yl)thiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-methyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

5-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)furo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

5-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)thieno[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-methyl-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

5-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-6-ethyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

5-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)thieno[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyridine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1,3-dimethyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*a*]pyridine;

4-((2*S*,5*S*)-4-(bis(4-fluorophenyl)methyl)-5-(methoxymethyl)-2-methylpiperazin-1-yl)thiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

2-((2*R*,5*S*)-1-(bis(4-fluorophenyl)methyl)-5-methyl-4-(thiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-4-yl)piperazin-2-yl)acetonitrile;

2-((2*R*,5*S*)-1-(bis(4-fluorophenyl)methyl)-4-(8-cyclopropylthiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-4-yl)-5-methylpiperazin-2-yl)acetonitrile;

2-((2*R*,5*S*)-1-(bis(4-fluorophenyl)methyl)-5-methyl-4-(1-methyl-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-2-yl)acetonitrile; and

(*R*)-3-(1-(bis(4-fluorophenyl)methyl)-4-(thiazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-4-yl)piperazin-2-yl)propanenitrile;

or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, which is selected from:

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(cyclopropylmethyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-diethylpiperazin-1-yl)-1-(cyclopropylmethyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

1-(cyclopropylmethyl)-4-((2*S*,5*R*)-4-((*S*)-1-(4-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

1-(cyclopropylmethyl)-4-((2*S*,5*R*)-4-((*R*)-1-(4-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

1-(cyclopropylmethyl)-4-((2*S*,5*R*)-4-((*S*)-(4-fluorophenyl)(5-(trifluoromethoxy)pyridin-2-yl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

1-(cyclopropylmethyl)-4-((2*S*,5*R*)-4-((*R*)-(4-fluorophenyl)(5-(trifluoromethoxy)pyridin-2-yl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-(4-fluorophenyl)(5-(trifluoromethoxy)pyridin-2-yl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-(4-fluorophenyl)(5-(trifluoromethoxy)pyridin-2-yl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine; and

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

or a pharmaceutically acceptable salt thereof.

60. The compound of claim 1, which is selected from:

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-diethylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-diethylpiperazin-1-yl)-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

2-(4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-diethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-diethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl-2-*d*)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl-2-*d*)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-2-methyl-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(4-(trifluoromethyl)phenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3-chloro-4-fluorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(3-fluoro-4-(trifluoromethyl)phenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-(3,3-difluorocyclobutyl)(3,4-difluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-(3,3-difluorocyclobutyl)(3,4-difluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-(3,4-dichlorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-(3,4-dichlorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((4-chloro-3-fluorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((4-chloro-3-methylphenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(3,4,5-trifluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(2,5-difluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(3-(difluoromethyl)-4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(3-methyl-4-(trifluoromethyl)phenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((2,5-difluoro-4-(trifluoromethyl)phenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3-chloro-2,4-difluorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3-chloro-4-(trifluoromethyl)phenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((4-chloro-3-(trifluoromethyl)phenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((4-chlorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((4-bromophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3-bromo-4-fluorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((4-bromo-3-fluorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-4-((4-chlorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-4-((4-bromophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-4-((4-chlorophenyl)(3,3-difluorocyclobutyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-2,5-dimethyl-4-((*S*)-2-methyl-1-(4-(trifluoromethyl)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-2,5-dimethyl-4-((*R*)-2-methyl-1-(4-(trifluoromethyl)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-2,5-dimethyl-4-((*S*)-2-methyl-1-(3-(trifluoromethyl)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-2,5-dimethyl-4-((*R*)-2-methyl-1-(3-(trifluoromethyl)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(2-fluoro-4-(trifluoromethyl)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(2-fluoro-4-(trifluoromethyl)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(4-(difluoromethyl)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(4-(difluoromethyl)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(4-(difluoromethoxy)-2-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(4-(difluoromethoxy)-2-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(4-methoxyphenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(4-methoxyphenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(4-(difluoromethoxy)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(4-(difluoromethoxy)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(1-(4-(difluoromethyl)-3-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(1-(3-(difluoromethyl)-4-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(1-(3-chloro-4-(trifluoromethyl)phenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(3-chloro-4-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(3-chloro-4-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(4-chlorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(4-chlorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-4-((*S*)-1-(4-chlorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-4-((*R*)-1-(4-chlorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-4-((4-(difluoromethyl)phenyl)(4-methoxyphenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(3-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(3-fluorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(3-chlorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(3-chlorophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*S*)-1-(3-methoxyphenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(3-methoxyphenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-4-(bis(4-(difluoromethyl)phenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-2,5-dimethyl-4-((*S*)-(4-(trifluoromethyl)phenyl)(5-(trifluoromethyl)pyridin-2-yl)methyl)piperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

2-(4-((2*S*,5*R*)-2,5-dimethyl-4-((*R*)-(4-(trifluoromethyl)phenyl)(5-(trifluoromethyl)pyridin-2-yl)methyl)piperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-4-((*S*)-(5-fluoro-6-(trifluoromethyl)pyridin-2-yl)(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-(5-fluoro-6-(trifluoromethyl)pyridin-2-yl)(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

2-(4-((2*S*,5*R*)-4-(bis(4-chlorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-4-(bis(4-bromophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-4-(bis(4-bromophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-4-(bis(4-bromophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-(bis(4-bromophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

2-(4-((2*S*,5*R*)-4-(bis(5-(trifluoromethyl)pyridin-2-yl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-4-((3-chloro-4-fluorophenyl)((*trans*)-3-(trifluoromethyl)cyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-4-((3-chloro-4-fluorophenyl)((*trans*)-3-(trifluoromethyl)cyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-b]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-2,5-dimethyl-4-(((*trans*)-3-(trifluoromethyl)cyclobutyl)(4-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-2,5-dimethyl-4-(((*trans*)-3-(trifluoromethyl)cyclobutyl)(4-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

4-((2*S*,5*R*)-4-((4,4-difluorocyclohexyl)(4-(trifluoromethyl)phenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-2,5-dimethyl-4-((*S*)-2-methyl-1-(4-(trifluoromethoxy)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-2,5-dimethyl-4-((*R*)-2-methyl-1-(4-(trifluoromethoxy)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(4-fluorophenyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

4-((2*S*,5*R*)-4-((4-chlorophenyl)(3,3-difluorocyclobutyl)methyl)-5-ethyl-2-methylpiperazin-1-yl)-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine;

((2*S*,5*S*)-1-((3,3-difluorocyclobutyl)(4-(trifluoromethyl)phenyl)methyl)-5-methyl-4-(2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-2-yl)methanol;

(*R*)-1-((2*S*,5*S*)-1-(bis(4-fluorophenyl)methyl)-5-methyl-4-(2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-2-yl)ethan-1-ol;

(*S*)-1-((2*S*,5*S*)-1-(bis(4-fluorophenyl)methyl)-5-methyl-4-(2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-2-yl)ethan-1-ol;

2-((2*R*,5*S*)-2-ethyl-5-methyl-4-(2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-1-yl)-2,2-bis(4-fluorophenyl)ethan-1-ol;

4-((2*S*,5*R*)-4-((*S*)-1-(4-(difluoromethoxy)phenyl)-2-methylpropyl)-5-ethyl-2-methylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(4-(difluoromethoxy)phenyl)-2-methylpropyl)-5-ethyl-2-methylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-5-ethyl-2-methyl-4-((*S*)-2-methyl-1-(4-(trifluoromethyl)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-5-ethyl-2-methyl-4-((*R*)-2-methyl-1-(4-(trifluoromethyl)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-5-ethyl-2-methyl-4-((*S*)-2-methyl-1-(4-(trifluoromethoxy)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-5-ethyl-2-methyl-4-((*R*)-2-methyl-1-(4-(trifluoromethoxy)phenyl)propyl)piperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-(((2*R*,5*S*)-2-ethyl-5-methyl-4-(2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-1-yl)(4-fluorophenyl)methyl)benzonitrile;

4-(((2*R*,5*S*)-2-ethyl-5-methyl-4-(2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-1-yl)(4-fluorophenyl)methyl)benzonitrile;

4-((2*S*,5*R*)-4-(bis(4-(trifluoromethyl)phenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3,3-difluorocyclobutyl)(4-(difluoromethyl)-3-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

2-(4-((2*S*,5*R*)-4-((4-chloro-3-fluorophenyl)(3,3-difluorocyclobutyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine;

((2*S*,5*S*)-1-(bis(4-chlorophenyl)methyl)-5-methyl-4-(2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-4-yl)piperazin-2-yl)methanol;

4-((2*S*,5*R*)-4-((*S*)-1-(4-bromophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((*R*)-1-(4-bromophenyl)-2-methylpropyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

4-((2*S*,5*R*)-4-((3-chloro-4-fluorophenyl)(4-chlorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine; and

4-((2*S*,5*R*)-4-((3-chloro-4-fluorophenyl)(4-bromophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-(((*S*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,4]triazolo[3,4-*b*]purine;

or a pharmaceutically acceptable salt thereof.

61. A compound, which is 2-(4-((2*S*,5*R*)-4-(Bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl)-*N*,*N*-dimethylethan-1-amine, or a pharmaceutically acceptable salt thereof.

62. A compound, which is 4-((2*S*,5*R*)-4-(Bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1-(((*R*)-tetrahydrofuran-2-yl)methyl)-1*H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine, or a pharmaceutically acceptable salt thereof.

63. A compound, which is 2-(4-((2*S*,5*R*)-4-(bis(4-fluorophenyl)methyl)-2,5-dimethylpiperazin-1-yl)-1*H*-[1,2,4]triazolo[3,4-*b*]purin-1-yl-2-*d*)-*N*,*N*-dimethylethan-1-amine, or a pharmaceutically acceptable salt thereof.

64. The compound of any of claims 1 to 63, or a pharmaceutically acceptable salt thereof, wherein the compound is deuterated.

65. A pharmaceutical composition, comprising a compound of any one of claims 1 to 64, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

66. A method of inhibiting an activity of a diacylglycerol kinase, comprising contacting *in vitro* the kinase with a compound of any one of claims 1 to 64, or a pharmaceutically acceptable salt thereof.

67. Use of a compound of any one of claims 1 to 64, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

68. The use of claim 67, wherein the cancer is non-small cell lung cancer, bladder urothelial carcinoma, esophageal carcinoma, stomach adenocarcinoma, mesothelioma, liver hepatocellular carcinoma, diffuse large B cell lymphoma, kidney renal clear cell carcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, and melanoma.

69. The use of claim 68, wherein the melanoma is metastatic melanoma.