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(54) Title: TRICYCLIC UREA COMPOUNDS AS JAK2 V617F INHIBITORS

(57) Abstract: The present application provides tricyclic urea compounds that modulate the activity of the V617F variant of JAK2, which are useful in the treatment of various diseases, including cancer.

TRICYCLIC UREA COMPOUNDS AS JAK2 V617F INHIBITORS

TECHNICAL FIELD

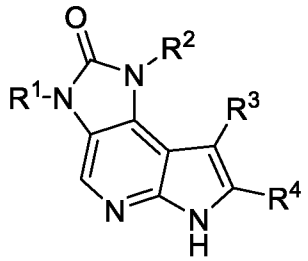
The present invention provides tricyclic urea compounds that modulate the activity of the V617F variant of JAK2 and are useful in the treatment of diseases related to the V617F variant of JAK2, including cancer.

BACKGROUND

Janus kinase (JAK) 2 plays pivotal roles in signaling by several cytokine receptors. The mutant JAK2 V617F is the most common molecular event associated with myeloproliferative neoplasms. Selective targeting of the JAK2 V617F mutant may be useful for treating various pathologies, while sparing essential JAK2 functions. This application is directed to this need and others.

SUMMARY

The present invention relates to, *inter alia*, compounds of Formula I:



I

or pharmaceutically acceptable salts thereof, wherein constituent members are defined herein.

The present invention further provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention further provides methods of inhibiting an activity of the V617F variant of JAK2 kinase comprising contacting the kinase with a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating a disease or a disorder associated with expression or activity of the V617F variant of JAK2 kinase

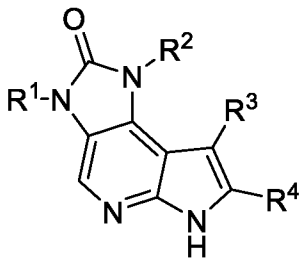
in a patient by administering to a patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

The present invention further provides use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in any of the methods described herein.

DETAILED DESCRIPTION

The present application provides compounds of Formula I:



I

or pharmaceutically acceptable salts thereof, wherein:

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

each R^{1A} is independently selected from halo, oxo, CN, NO_2, OR^{a11}, SR^{a11}, $NHOR^{a11}$, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)NR^{c11}(OR^{a11})$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $C(=NR^{e11})R^{b11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})R^{b11}$, $NR^{c11}S(O)R^{b11}$, $NR^{c11}S(O)NR^{c11}R^{d11}$, $NR^{c11}S(O)_2R^{b11}$, $NR^{c11}S(O)(=NR^{e11})R^{b11}$, $NR^{c11}S(O)_2NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$, $OS(O)(=NR^{e11})R^{b11}$, and $OS(O)_2R^{b11}$;

each R^{a11}, R^{b11}, R^{c11}, and R^{d11} is independently selected from H, 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^{a11}, R^{b11}, R^{c11} and R^{d11} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^M 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, and C_{2-6} alkynyl;

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

each R^{2A} 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^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, $OS(O)_2R^{b21}$, SF_5, $P(O)R^{f21}R^{g21}$, $OP(O)(OR^{h21})(OR^{i21})$, $P(O)(OR^{h21})(OR^{i21})$, and $BR^{j21}R^{k21}$, 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^{2A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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, 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^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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 5-10 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, or 4 independently selected R^{2B} 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, 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^{b21} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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, 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^{f21} and R^{g21} is independently selected from H, 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^{h21} and R^{i21} 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-;

each R^{j21} and R^{k21} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j21} and R^{k21} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{2B} 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^{a22}, SR^{a22}, $NHOR^{a22}$, $C(O)R^{b22}$, $C(O)NR^{c22}R^{d22}$, $C(O)NR^{c22}(OR^{a22})$, $C(O)OR^{a22}$, $OC(O)R^{b22}$, $OC(O)NR^{c22}R^{d22}$, $NR^{c22}R^{d22}$, $NR^{c22}NR^{c22}R^{d22}$, $NR^{c22}C(O)R^{b22}$, $NR^{c22}C(O)OR^{a22}$, $NR^{c22}C(O)NR^{c22}R^{d22}$, $C(=NR^{e22})R^{b22}$, $C(=NR^{e22})NR^{c22}R^{d22}$, $NR^{c22}C(=NR^{e22})NR^{c22}R^{d22}$, $NR^{c22}C(=NR^{e22})R^{b22}$, $NR^{c22}S(O)R^{b22}$, $NR^{c22}S(O)NR^{c22}R^{d22}$, $NR^{c22}S(O)_2R^{b22}$, $NR^{c22}S(O)(=NR^{e22})R^{b22}$, $NR^{c22}S(O)_2NR^{c22}R^{d22}$, $S(O)R^{b22}$, $S(O)NR^{c22}R^{d22}$, $S(O)_2R^{b22}$, $S(O)_2NR^{c22}R^{d22}$, $OS(O)(=NR^{e22})R^{b22}$, $OS(O)_2R^{b22}$, SF_5, $P(O)R^{f22}R^{g22}$, $OP(O)(OR^{h22})(OR^{i22})$, $P(O)(OR^{h22})(OR^{i22})$, and $BR^{j22}R^{k22}$, 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^{2B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{a22}, R^{c22}, and R^{d22} 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^{a22}, R^{c22} and R^{d22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

or, any R^{c22} and R^{d22} 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, or 4 independently selected R^{2C} substituents;

each R^{b22} 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^{b22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{e22} 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^{f22} and R^{g22} is independently selected from H, 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^{h22} and R^{i22} 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-;

each R^{j22} and R^{k22} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j22} and R^{k22} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{2C} 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^{a23}, SR^{a23}, $NHOR^{a23}$, $C(O)R^{b23}$, $C(O)NR^{c23}R^{d23}$, $C(O)NR^{c23}(OR^{a23})$, $C(O)OR^{a23}$, $OC(O)R^{b23}$, $OC(O)NR^{c23}R^{d23}$, $NR^{c23}R^{d23}$, $NR^{c23}NR^{c23}R^{d23}$, $NR^{c23}C(O)R^{b23}$, $NR^{c23}C(O)OR^{a23}$, $NR^{c23}C(O)NR^{c23}R^{d23}$, $C(=NR^{e23})R^{b23}$, $C(=NR^{e23})NR^{c23}R^{d23}$, $NR^{c23}C(=NR^{e23})NR^{c23}R^{d23}$, $NR^{c23}C(=NR^{e23})R^{b23}$, $NR^{c23}S(O)R^{b23}$, $NR^{c23}S(O)NR^{c23}R^{d23}$, $NR^{c23}S(O)_2R^{b23}$, $NR^{c23}S(O)(=NR^{e23})R^{b23}$, $NR^{c23}S(O)_2NR^{c23}R^{d23}$, $S(O)R^{b23}$, $S(O)NR^{c23}R^{d23}$, $S(O)_2R^{b23}$, $S(O)_2NR^{c23}R^{d23}$, $OS(O)(=NR^{e23})R^{b23}$, and $OS(O)_2R^{b23}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{2C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a23}, R^{c23}, and R^{d23} 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^{a23}, R^{c23} and R^{d23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c23} and R^{d23} 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^{b23} 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^{b23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e23} 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}, $NHOR^{a3}$, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)NR^{c3}(OR^{a3})$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $C(=NR^{e3})R^{b3}$, $C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})R^{b3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)(=NR^{e3})R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, $OS(O)(=NR^{e3})R^{b3}$, $OS(O)_2R^{b3}$, SF_5, $P(O)R^{f3}R^{g3}$, $OP(O)(OR^{h3})(OR^{i3})$, $P(O)(OR^{h3})(OR^{i3})$, and $BR^{j3}R^{k3}$, 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, or 4 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-;

each R^{f3} and R^{g3} is independently selected from H, 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^{h3} and R^{i3} 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-;

each R^{j3} and R^{k3} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j3} and R^{k3} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3A} 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^{a31}, SR^{a31}, $NHOR^{a31}$, $C(O)R^{b31}$, $C(O)NR^{c31}R^{d31}$, $C(O)NR^{c31}(OR^{a31})$, $C(O)OR^{a31}$, $OC(O)R^{b31}$, $OC(O)NR^{c31}R^{d31}$, $NR^{c31}R^{d31}$, $NR^{c31}NR^{c31}R^{d31}$, $NR^{c31}C(O)R^{b31}$, $NR^{c31}C(O)OR^{a31}$, $NR^{c31}C(O)NR^{c31}R^{d31}$, $C(=NR^{e31})R^{b31}$, $C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})R^{b31}$, $NR^{c31}S(O)R^{b31}$, $NR^{c31}S(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)_2R^{b31}$, $NR^{c31}S(O)(=NR^{e31})R^{b31}$, $NR^{c31}S(O)_2NR^{c31}R^{d31}$, $S(O)R^{b31}$, $S(O)NR^{c31}R^{d31}$, $S(O)_2R^{b31}$, $S(O)_2NR^{c31}R^{d31}$, $OS(O)(=NR^{e31})R^{b31}$, $OS(O)_2R^{b31}$, SF_5, $P(O)R^{f31}R^{g31}$, $OP(O)(OR^{h31})(OR^{i31})$, $P(O)(OR^{h31})(OR^{i31})$, and $BR^{j31}R^{k31}$, 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^{3A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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, 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^{a31}, R^{c31} and R^{d31} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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 5-10 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, or 4 independently selected R^{3B} 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, 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^{b31} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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-;

each R^{f31} and R^{g31} is independently selected from H, 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^{h31} and R^{i31} 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-;

each R^{j31} and R^{k31} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j31} and R^{k31} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3B} 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^{a32}, SR^{a32}, $NHOR^{a32}$, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, $C(O)NR^{c32}(OR^{a32})$, $C(O)OR^{a32}$, $OC(O)R^{b32}$, $OC(O)NR^{c32}R^{d32}$, $NR^{c32}R^{d32}$, $NR^{c32}NR^{c32}R^{d32}$, $NR^{c32}C(O)R^{b32}$, $NR^{c32}C(O)OR^{a32}$, $NR^{c32}C(O)NR^{c32}R^{d32}$, $C(=NR^{e32})R^{b32}$, $C(=NR^{e32})NR^{c32}R^{d32}$, $NR^{c32}C(=NR^{e32})NR^{c32}R^{d32}$, $NR^{c32}C(=NR^{e32})R^{b32}$, $NR^{c32}S(O)R^{b32}$, $NR^{c32}S(O)NR^{c32}R^{d32}$, $NR^{c32}S(O)_2R^{b32}$, $NR^{c32}S(O)(=NR^{e32})R^{b32}$, $NR^{c32}S(O)_2NR^{c32}R^{d32}$, $S(O)R^{b32}$, $S(O)NR^{c32}R^{d32}$, $S(O)_2R^{b32}$, $S(O)_2NR^{c32}R^{d32}$, $OS(O)(=NR^{e32})R^{b32}$, $OS(O)_2R^{b32}$, SF_5, $P(O)R^{f32}R^{g32}$, $OP(O)(OR^{h32})(OR^{i32})$, $P(O)(OR^{h32})(OR^{i32})$, and $BR^{j32}R^{k32}$, 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^{3B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

each R^{a32}, R^{c32}, and R^{d32} 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^{a32}, R^{c32} and R^{d32} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

or, any R^{c32} and R^{d32} 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, or 4 independently selected R^{3C} substituents;

each R^{b32} 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^{b32} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

each R^{e32} 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^{f32} and R^{g32} is independently selected from H, 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^{h32} and R^{i32} 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-;

each R^{j32} and R^{k32} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j32} and R^{k32} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3C} 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^{a33}, SR^{a33}, $NHOR^{a33}$, $C(O)R^{b33}$, $C(O)NR^{c33}R^{d33}$, $C(O)NR^{c33}(OR^{a33})$, $C(O)OR^{a33}$, $OC(O)R^{b33}$, $OC(O)NR^{c33}R^{d33}$, $NR^{c33}R^{d33}$, $NR^{c33}NR^{c33}R^{d33}$, $NR^{c33}C(O)R^{b33}$, $NR^{c33}C(O)OR^{a33}$, $NR^{c33}C(O)NR^{c33}R^{d33}$, $C(=NR^{e33})R^{b33}$, $C(=NR^{e33})NR^{c33}R^{d33}$, $NR^{c33}C(=NR^{e33})NR^{c33}R^{d33}$, $NR^{c33}C(=NR^{e33})R^{b33}$, $NR^{c33}S(O)R^{b33}$, $NR^{c33}S(O)NR^{c33}R^{d33}$, $NR^{c33}S(O)_2R^{b33}$, $NR^{c33}S(O)(=NR^{e33})R^{b33}$, $NR^{c33}S(O)_2NR^{c33}R^{d33}$, $S(O)R^{b33}$, $S(O)NR^{c33}R^{d33}$, $S(O)_2R^{b33}$, $S(O)_2NR^{c33}R^{d33}$, $OS(O)(=NR^{e33})R^{b33}$, and $OS(O)_2R^{b33}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{3C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a33}, R^{c33}, and R^{d33} 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^{a33}, R^{c33} and R^{d33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c33} and R^{d33} 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^{b33} 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^{b33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e33} 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^4 is selected from 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}, $NHOR^{a4}$, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)NR^{c4}(OR^{a4})$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $C(=NR^{e4})R^{b4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})R^{b4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)(=NR^{e4})R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, $OS(O)(=NR^{e4})R^{b4}$, $OS(O)_2R^{b4}$, SF_5, $P(O)R^{f4}R^{g4}$, $OP(O)(OR^{h4})(OR^{i4})$, $P(O)(OR^{h4})(OR^{i4})$, and $BR^{j4}R^{k4}$, 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, or 4 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-;

each R^{f4} and R^{g4} is independently selected from H, 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^{h4} and R^{i4} 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-;

each R^{j4} and R^{k4} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j4} and R^{k4} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4A} 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^{a41}, SR^{a41}, $NHOR^{a41}$, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, $C(O)NR^{c41}(OR^{a41})$, $C(O)OR^{a41}$, $OC(O)R^{b41}$, $OC(O)NR^{c41}R^{d41}$, $NR^{c41}R^{d41}$, $NR^{c41}NR^{c41}R^{d41}$, $NR^{c41}C(O)R^{b41}$, $NR^{c41}C(O)OR^{a41}$, $NR^{c41}C(O)NR^{c41}R^{d41}$, $C(=NR^{e41})R^{b41}$, $C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})R^{b41}$, $NR^{c41}S(O)R^{b41}$, $NR^{c41}S(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)_2R^{b41}$, $NR^{c41}S(O)(=NR^{e41})R^{b41}$, $NR^{c41}S(O)_2NR^{c41}R^{d41}$, $S(O)R^{b41}$, $S(O)NR^{c41}R^{d41}$, $S(O)_2R^{b41}$, $S(O)_2NR^{c41}R^{d41}$, $OS(O)(=NR^{e41})R^{b41}$, $OS(O)_2R^{b41}$, SF_5, $P(O)R^{f41}R^{g41}$, $OP(O)(OR^{h41})(OR^{i41})$, $P(O)(OR^{h41})(OR^{i41})$, and $BR^{j41}R^{k41}$, 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^{4A} are

each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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, 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^{a41}, R^{c41} and R^{d41} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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 5-10 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, or 4 independently selected R^{4B} 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, 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^{b41} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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, 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^{f41} and R^{g41} is independently selected from H, 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^{h41} and R^{i41} 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-;

each R^{j41} and R^{k41} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j41} and R^{k41} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4B} 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^{a42}, SR^{a42}, $NHOR^{a42}$, $C(O)R^{b42}$, $C(O)NR^{c42}R^{d42}$, $C(O)NR^{c42}(OR^{a42})$, $C(O)OR^{a42}$, $OC(O)R^{b42}$, $OC(O)NR^{c42}R^{d42}$, $NR^{c42}R^{d42}$, $NR^{c42}NR^{c42}R^{d42}$, $NR^{c42}C(O)R^{b42}$, $NR^{c42}C(O)OR^{a42}$, $NR^{c42}C(O)NR^{c42}R^{d42}$, $C(=NR^{e42})R^{b42}$, $C(=NR^{e42})NR^{c42}R^{d42}$, $NR^{c42}C(=NR^{e42})NR^{c42}R^{d42}$, $NR^{c42}C(=NR^{e42})R^{b42}$, $NR^{c42}S(O)R^{b42}$, $NR^{c42}S(O)NR^{c42}R^{d42}$, $NR^{c42}S(O)_2R^{b42}$, $NR^{c42}S(O)(=NR^{e42})R^{b42}$, $NR^{c42}S(O)_2NR^{c42}R^{d42}$, $S(O)R^{b42}$, $S(O)NR^{c42}R^{d42}$, $S(O)_2R^{b42}$, $S(O)_2NR^{c42}R^{d42}$, $OS(O)(=NR^{e42})R^{b42}$, $OS(O)_2R^{b42}$, SF_5, $P(O)R^{f42}R^{g42}$, $OP(O)(OR^{h42})(OR^{i42})$, $P(O)(OR^{h42})(OR^{i42})$, and $BR^{j42}R^{k42}$, 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^{4B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

each R^{a42}, R^{c42}, and R^{d42} 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^{a42}, R^{c42} and R^{d42} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

or, any R^{c42} and R^{d42} 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, or 4 independently selected R^{4C} substituents;

each R^{b42} 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^{b42} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

each R^{e42} 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^{f42} and R^{g42} is independently selected from H, 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^{h42} and R^{i42} 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-;

each R^{j42} and R^{k42} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j42} and R^{k42} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4C} 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^{a43}, SR^{a43}, $NHOR^{a43}$, $C(O)R^{b43}$, $C(O)NR^{c43}R^{d43}$, $C(O)NR^{c43}(OR^{a43})$, $C(O)OR^{a43}$, $OC(O)R^{b43}$, $OC(O)NR^{c43}R^{d43}$, $NR^{c43}R^{d43}$, $NR^{c43}NR^{c43}R^{d43}$, $NR^{c43}C(O)R^{b43}$, $NR^{c43}C(O)OR^{a43}$, $NR^{c43}C(O)NR^{c43}R^{d43}$, $C(=NR^{e43})R^{b43}$, $C(=NR^{e43})NR^{c43}R^{d43}$, $NR^{c43}C(=NR^{e43})NR^{c43}R^{d43}$, $NR^{c43}C(=NR^{e43})R^{b43}$, $NR^{c43}S(O)R^{b43}$, $NR^{c43}S(O)NR^{c43}R^{d43}$, $NR^{c43}S(O)_2R^{b43}$, $NR^{c43}S(O)(=NR^{e43})R^{b43}$, $NR^{c43}S(O)_2NR^{c43}R^{d43}$, $S(O)R^{b43}$, $S(O)NR^{c43}R^{d43}$, $S(O)_2R^{b43}$, $S(O)_2NR^{c43}R^{d43}$, $OS(O)(=NR^{e43})R^{b43}$, and $OS(O)_2R^{b43}$, 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^{4C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a43}, R^{c43}, and R^{d43} 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^{a43}, R^{c43} and R^{d43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c43} and R^{d43} 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^{b43} 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^{b43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e43} 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^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, 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-.

In some embodiments:

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

each R^{1A} is independently selected from D, halo, oxo, CN, NO_2, OR^{a11}, SR^{a11}, $NHOR^{a11}$, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)NR^{c11}(OR^{a11})$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $C(=NR^{e11})R^{b11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})R^{b11}$, $NR^{c11}S(O)R^{b11}$, $NR^{c11}S(O)NR^{c11}R^{d11}$, $NR^{c11}S(O)_2R^{b11}$, $NR^{c11}S(O)(=NR^{e11})R^{b11}$, $NR^{c11}S(O)_2NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$, $OS(O)(=NR^{e11})R^{b11}$, and $OS(O)_2R^{b11}$;

each R^{a11}, R^{b11}, R^{c11}, and R^{d11} is independently selected from H, 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^{a11}, R^{b11}, R^{c11} and R^{d11} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^M 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, and C_{2-6} alkynyl;

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

each R^{2A} is independently selected from D, 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^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$,

$NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, $OS(O)_2R^{b21}$, SF_5, $P(O)R^{f21}R^{g21}$, $OP(O)(OR^{h21})(OR^{i21})$, $P(O)(OR^{h21})(OR^{i21})$, and $BR^{j21}R^{k21}$, 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^{2A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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, 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^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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 5-10 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, or 4 independently selected R^{2B} 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, 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^{b21} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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, 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^{f21} and R^{g21} is independently selected from H, 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^{h21} and R^{i21} 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-;

each R^{j21} and R^{k21} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j21} and R^{k21} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{2B} is independently selected from D, 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^{a22}, SR^{a22}, $NHOR^{a22}$, $C(O)R^{b22}$, $C(O)NR^{c22}R^{d22}$, $C(O)NR^{c22}(OR^{a22})$, $C(O)OR^{a22}$, $OC(O)R^{b22}$, $OC(O)NR^{c22}R^{d22}$, $NR^{c22}R^{d22}$, $NR^{c22}NR^{c22}R^{d22}$, $NR^{c22}C(O)R^{b22}$, $NR^{c22}C(O)OR^{a22}$, $NR^{c22}C(O)NR^{c22}R^{d22}$, $C(=NR^{e22})R^{b22}$, $C(=NR^{e22})NR^{c22}R^{d22}$, $NR^{c22}C(=NR^{e22})NR^{c22}R^{d22}$, $NR^{c22}C(=NR^{e22})R^{b22}$, $NR^{c22}S(O)R^{b22}$, $NR^{c22}S(O)NR^{c22}R^{d22}$, $NR^{c22}S(O)_2R^{b22}$, $NR^{c22}S(O)(=NR^{e22})R^{b22}$, $NR^{c22}S(O)_2NR^{c22}R^{d22}$, $S(O)R^{b22}$, $S(O)NR^{c22}R^{d22}$, $S(O)_2R^{b22}$, $S(O)_2NR^{c22}R^{d22}$, $OS(O)(=NR^{e22})R^{b22}$, $OS(O)_2R^{b22}$, SF_5, $P(O)R^{f22}R^{g22}$, $OP(O)(OR^{h22})(OR^{i22})$, $P(O)(OR^{h22})(OR^{i22})$, and $BR^{j22}R^{k22}$, 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^{2B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{a22}, R^{c22}, and R^{d22} 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^{a22}, R^{c22} and R^{d22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

or, any R^{c22} and R^{d22} 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, or 4 independently selected R^{2C} substituents;

each R^{b22} 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^{b22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{e22} 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^{f22} and R^{g22} is independently selected from H, 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^{h22} and R^{i22} 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-;

each R^{j22} and R^{k22} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j22} and R^{k22} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{2C} is independently selected from D, 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^{a23}, SR^{a23}, $NHOR^{a23}$, $C(O)R^{b23}$, $C(O)NR^{c23}R^{d23}$, $C(O)NR^{c23}(OR^{a23})$, $C(O)OR^{a23}$, $OC(O)R^{b23}$, $OC(O)NR^{c23}R^{d23}$, $NR^{c23}R^{d23}$, $NR^{c23}NR^{c23}R^{d23}$, $NR^{c23}C(O)R^{b23}$, $NR^{c23}C(O)OR^{a23}$, $NR^{c23}C(O)NR^{c23}R^{d23}$, $C(=NR^{e23})R^{b23}$, $C(=NR^{e23})NR^{c23}R^{d23}$, $NR^{c23}C(=NR^{e23})NR^{c23}R^{d23}$, $NR^{c23}C(=NR^{e23})R^{b23}$, $NR^{c23}S(O)R^{b23}$, $NR^{c23}S(O)NR^{c23}R^{d23}$, $NR^{c23}S(O)_2R^{b23}$, $NR^{c23}S(O)(=NR^{e23})R^{b23}$, $NR^{c23}S(O)_2NR^{c23}R^{d23}$, $S(O)R^{b23}$, $S(O)NR^{c23}R^{d23}$, $S(O)_2R^{b23}$, $S(O)_2NR^{c23}R^{d23}$, $OS(O)(=NR^{e23})R^{b23}$, and $OS(O)_2R^{b23}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{2C}

are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a23}, R^{c23}, and R^{d23} 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^{a23}, R^{c23} and R^{d23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c23} and R^{d23} 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^{b23} 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^{b23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e23} 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, D, 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}, $NHOR^{a3}$, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)NR^{c3}(OR^{a3})$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $C(=NR^{e3})R^{b3}$, $C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})R^{b3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)(=NR^{e3})R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, $OS(O)(=NR^{e3})R^{b3}$, $OS(O)_2R^{b3}$, SF_5, $P(O)R^{f3}R^{g3}$, $OP(O)(OR^{h3})(OR^{i3})$, $P(O)(OR^{h3})(OR^{i3})$, and $BR^{j3}R^{k3}$, 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, or 4 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-;

each R^{f3} and R^{g3} is independently selected from H, 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^{h3} and R^{i3} 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-;

each R^{j3} and R^{k3} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j3} and R^{k3} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3A} is independently selected from D, 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^{a31}, SR^{a31}, $NHOR^{a31}$, $C(O)R^{b31}$, $C(O)NR^{c31}R^{d31}$, $C(O)NR^{c31}(OR^{a31})$, $C(O)OR^{a31}$, $OC(O)R^{b31}$, $OC(O)NR^{c31}R^{d31}$, $NR^{c31}R^{d31}$, $NR^{c31}NR^{c31}R^{d31}$, $NR^{c31}C(O)R^{b31}$, $NR^{c31}C(O)OR^{a31}$, $NR^{c31}C(O)NR^{c31}R^{d31}$,

$C(=NR^{e31})R^{b31}$, $C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})R^{b31}$, $NR^{c31}S(O)R^{b31}$, $NR^{c31}S(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)_2R^{b31}$, $NR^{c31}S(O)(=NR^{e31})R^{b31}$, $NR^{c31}S(O)_2NR^{c31}R^{d31}$, $S(O)R^{b31}$, $S(O)NR^{c31}R^{d31}$, $S(O)_2R^{b31}$, $S(O)_2NR^{c31}R^{d31}$, $OS(O)(=NR^{e31})R^{b31}$, $OS(O)_2R^{b31}$, SF_5, $P(O)R^{f31}R^{g31}$, $OP(O)(OR^{h31})(OR^{i31})$, $P(O)(OR^{h31})(OR^{i31})$, and $BR^{j31}R^{k31}$, 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^{3A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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, 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^{a31}, R^{c31} and R^{d31} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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 5-10 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, or 4 independently selected R^{3B} 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, 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^{b31} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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-;

each R^{f31} and R^{g31} is independently selected from H, 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^{h31} and R^{i31} 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-;

each R^{j31} and R^{k31} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j31} and R^{k31} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3B} is independently selected from D, 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^{a32}, SR^{a32}, $NHOR^{a32}$, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, $C(O)NR^{c32}(OR^{a32})$, $C(O)OR^{a32}$, $OC(O)R^{b32}$, $OC(O)NR^{c32}R^{d32}$, $NR^{c32}R^{d32}$, $NR^{c32}NR^{c32}R^{d32}$, $NR^{c32}C(O)R^{b32}$, $NR^{c32}C(O)OR^{a32}$, $NR^{c32}C(O)NR^{c32}R^{d32}$, $C(=NR^{e32})R^{b32}$, $C(=NR^{e32})NR^{c32}R^{d32}$, $NR^{c32}C(=NR^{e32})NR^{c32}R^{d32}$, $NR^{c32}C(=NR^{e32})R^{b32}$, $NR^{c32}S(O)R^{b32}$, $NR^{c32}S(O)NR^{c32}R^{d32}$, $NR^{c32}S(O)_2R^{b32}$, $NR^{c32}S(O)(=NR^{e32})R^{b32}$, $NR^{c32}S(O)_2NR^{c32}R^{d32}$, $S(O)R^{b32}$, $S(O)NR^{c32}R^{d32}$, $S(O)_2R^{b32}$,

$S(O)_2NR^{c32}R^{d32}$, $OS(O)(=NR^{e32})R^{b32}$, $OS(O)_2R^{b32}$, SF_5, $P(O)R^{f32}R^{g32}$, $OP(O)(OR^{h32})(OR^{i32})$, $P(O)(OR^{h32})(OR^{i32})$, and $BR^{j32}R^{k32}$, 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^{3B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

each R^{a32}, R^{c32}, and R^{d32} 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^{a32}, R^{c32} and R^{d32} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

or, any R^{c32} and R^{d32} 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, or 4 independently selected R^{3C} substituents;

each R^{b32} 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^{b32} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

each R^{e32} 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^{f32} and R^{g32} is independently selected from H, 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^{h32} and R^{i32} 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-;

each R^{j32} and R^{k32} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j32} and R^{k32} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3C} is independently selected from D, 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^{a33}, SR^{a33}, $NHOR^{a33}$, $C(O)R^{b33}$, $C(O)NR^{c33}R^{d33}$, $C(O)NR^{c33}(OR^{a33})$, $C(O)OR^{a33}$, $OC(O)R^{b33}$, $OC(O)NR^{c33}R^{d33}$, $NR^{c33}R^{d33}$, $NR^{c33}NR^{c33}R^{d33}$, $NR^{c33}C(O)R^{b33}$, $NR^{c33}C(O)OR^{a33}$, $NR^{c33}C(O)NR^{c33}R^{d33}$, $C(=NR^{e33})R^{b33}$, $C(=NR^{e33})NR^{c33}R^{d33}$, $NR^{c33}C(=NR^{e33})NR^{c33}R^{d33}$, $NR^{c33}C(=NR^{e33})R^{b33}$, $NR^{c33}S(O)R^{b33}$, $NR^{c33}S(O)NR^{c33}R^{d33}$, $NR^{c33}S(O)_2R^{b33}$, $NR^{c33}S(O)(=NR^{e33})R^{b33}$, $NR^{c33}S(O)_2NR^{c33}R^{d33}$, $S(O)R^{b33}$, $S(O)NR^{c33}R^{d33}$, $S(O)_2R^{b33}$, $S(O)_2NR^{c33}R^{d33}$, $OS(O)(=NR^{e33})R^{b33}$, and $OS(O)_2R^{b33}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{3C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a33}, R^{c33}, and R^{d33} 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^{a33}, R^{c33} and R^{d33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c33} and R^{d33} 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^{b33} 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^{b33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e33} 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^4 is selected from 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}, $NHOR^{a4}$, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)NR^{c4}(OR^{a4})$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $C(=NR^{e4})R^{b4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})R^{b4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)(=NR^{e4})R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, $OS(O)(=NR^{e4})R^{b4}$, $OS(O)_2R^{b4}$, SF_5, $P(O)R^{f4}R^{g4}$, $OP(O)(OR^{h4})(OR^{i4})$, $P(O)(OR^{h4})(OR^{i4})$, and $BR^{j4}R^{k4}$, 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, or 4 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-;

each R^{f4} and R^{g4} is independently selected from H, 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^{h4} and R^{i4} 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-;

each R^{j4} and R^{k4} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j4} and R^{k4} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4A} is independently selected from D, 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^{a41}, SR^{a41}, $NHOR^{a41}$, $C(O)R^{b41}$,

$C(O)NR^{c41}R^{d41}$, $C(O)NR^{c41}(OR^{a41})$, $C(O)OR^{a41}$, $OC(O)R^{b41}$, $OC(O)NR^{c41}R^{d41}$, $NR^{c41}R^{d41}$, $NR^{c41}NR^{c41}R^{d41}$, $NR^{c41}C(O)R^{b41}$, $NR^{c41}C(O)OR^{a41}$, $NR^{c41}C(O)NR^{c41}R^{d41}$, $C(=NR^{e41})R^{b41}$, $C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})R^{b41}$, $NR^{c41}S(O)R^{b41}$, $NR^{c41}S(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)_2R^{b41}$, $NR^{c41}S(O)(=NR^{e41})R^{b41}$, $NR^{c41}S(O)_2NR^{c41}R^{d41}$, $S(O)R^{b41}$, $S(O)NR^{c41}R^{d41}$, $S(O)_2R^{b41}$, $S(O)_2NR^{c41}R^{d41}$, $OS(O)(=NR^{e41})R^{b41}$, $OS(O)_2R^{b41}$, SF_5, $P(O)R^{f41}R^{g41}$, $OP(O)(OR^{h41})(OR^{i41})$, $P(O)(OR^{h41})(OR^{i41})$, and $BR^{j41}R^{k41}$, 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^{4A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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, 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^{a41}, R^{c41} and R^{d41} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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 5-10 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, or 4 independently selected R^{4B} 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, 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^{b41} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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, 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^{f41} and R^{g41} is independently selected from H, 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^{h41} and R^{i41} 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-;

each R^{j41} and R^{k41} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j41} and R^{k41} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4B} is independently selected from D, 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^{a42}, SR^{a42}, $NHOR^{a42}$, $C(O)R^{b42}$, $C(O)NR^{c42}R^{d42}$, $C(O)NR^{c42}(OR^{a42})$, $C(O)OR^{a42}$, $OC(O)R^{b42}$, $OC(O)NR^{c42}R^{d42}$, $NR^{c42}R^{d42}$, $NR^{c42}NR^{c42}R^{d42}$, $NR^{c42}C(O)R^{b42}$, $NR^{c42}C(O)OR^{a42}$, $NR^{c42}C(O)NR^{c42}R^{d42}$, $C(=NR^{e42})R^{b42}$, $C(=NR^{e42})NR^{c42}R^{d42}$, $NR^{c42}C(=NR^{e42})NR^{c42}R^{d42}$,

$NR^{c42}C(=NR^{e42})R^{b42}$, $NR^{c42}S(O)R^{b42}$, $NR^{c42}S(O)NR^{c42}R^{d42}$, $NR^{c42}S(O)_2R^{b42}$, $NR^{c42}S(O)(=NR^{e42})R^{b42}$, $NR^{c42}S(O)_2NR^{c42}R^{d42}$, $S(O)R^{b42}$, $S(O)NR^{c42}R^{d42}$, $S(O)_2R^{b42}$, $S(O)_2NR^{c42}R^{d42}$, $OS(O)(=NR^{e42})R^{b42}$, $OS(O)_2R^{b42}$, SF_5, $P(O)R^{f42}R^{g42}$, $OP(O)(OR^{h42})(OR^{i42})$, $P(O)(OR^{h42})(OR^{i42})$, and $BR^{j42}R^{k42}$, 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^{4B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

each R^{a42}, R^{c42}, and R^{d42} 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^{a42}, R^{c42} and R^{d42} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

or, any R^{c42} and R^{d42} 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, or 4 independently selected R^{4C} substituents;

each R^{b42} 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^{b42} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

each R^{e42} 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^{f42} and R^{g42} is independently selected from H, 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^{h42} and R^{i42} 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-;

each R^{j42} and R^{k42} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j42} and R^{k42} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4C} is independently selected from D, 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^{a43}, SR^{a43}, $NHOR^{a43}$, $C(O)R^{b43}$, $C(O)NR^{c43}R^{d43}$, $C(O)NR^{c43}(OR^{a43})$, $C(O)OR^{a43}$, $OC(O)R^{b43}$, $OC(O)NR^{c43}R^{d43}$, $NR^{c43}R^{d43}$, $NR^{c43}NR^{c43}R^{d43}$, $NR^{c43}C(O)R^{b43}$, $NR^{c43}C(O)OR^{a43}$, $NR^{c43}C(O)NR^{c43}R^{d43}$, $C(=NR^{e43})R^{b43}$, $C(=NR^{e43})NR^{c43}R^{d43}$, $NR^{c43}C(=NR^{e43})NR^{c43}R^{d43}$, $NR^{c43}C(=NR^{e43})R^{b43}$, $NR^{c43}S(O)R^{b43}$, $NR^{c43}S(O)NR^{c43}R^{d43}$, $NR^{c43}S(O)_2R^{b43}$, $NR^{c43}S(O)(=NR^{e43})R^{b43}$, $NR^{c43}S(O)_2NR^{c43}R^{d43}$, $S(O)R^{b43}$, $S(O)NR^{c43}R^{d43}$, $S(O)_2R^{b43}$,

$S(O)_2NR^{c43}R^{d43}$, $OS(O)(=NR^{e43})R^{b43}$, and $OS(O)_2R^{b43}$, 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^{4C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a43}, R^{c43}, and R^{d43} 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^{a43}, R^{c43} and R^{d43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c43} and R^{d43} 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^{b43} 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^{b43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e43} 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^M is independently selected from H, D, 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, 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-.

In some embodiments:

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

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

each R^{2A} 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^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, , 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^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} 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, 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^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} 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 5-10 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, or 4 independently selected R^{2B} 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, 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^{b21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

each R^{2B} 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^{a22}, SR^{a22}, $C(O)R^{b22}$, $C(O)NR^{c22}R^{d22}$, $C(O)NR^{c22}(OR^{a22})$, $C(O)OR^{a22}$, $OC(O)R^{b22}$, $OC(O)NR^{c22}R^{d22}$, $NR^{c22}R^{d22}$, $NR^{c22}C(O)R^{b22}$, $NR^{c22}C(O)OR^{a22}$, $NR^{c22}C(O)NR^{c22}R^{d22}$, $NR^{c22}S(O)R^{b22}$, $NR^{c22}S(O)NR^{c22}R^{d22}$, $NR^{c22}S(O)_2R^{b22}$, $NR^{c22}S(O)_2NR^{c22}R^{d22}$, $S(O)R^{b22}$, $S(O)NR^{c22}R^{d22}$, $S(O)_2R^{b22}$, and $S(O)_2NR^{c22}R^{d22}$, 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^{2B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2C} substituents;

each R^{a22}, R^{c22}, and R^{d22} 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^{a22}, R^{c22} and R^{d22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

or, any R^{c22} and R^{d22} 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, or 4 independently selected R^{2C} substituents;

each R^{b22} 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^{b22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{2C} 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^{a23}, SR^{a23}, $C(O)R^{b23}$, $C(O)NR^{c23}R^{d23}$, $C(O)NR^{c23}(OR^{a23})$, $C(O)OR^{a23}$, $OC(O)R^{b23}$, $OC(O)NR^{c23}R^{d23}$, $NR^{c23}R^{d23}$, $NR^{c23}C(O)R^{b23}$, $NR^{c23}C(O)OR^{a23}$, $NR^{c23}C(O)NR^{c23}R^{d23}$, $NR^{c23}S(O)R^{b23}$, $NR^{c23}S(O)NR^{c23}R^{d23}$, $NR^{c23}S(O)_2R^{b23}$, $NR^{c23}S(O)_2NR^{c23}R^{d23}$, $S(O)R^{b23}$, $S(O)NR^{c23}R^{d23}$, $S(O)_2R^{b23}$, and $S(O)_2NR^{c23}R^{d23}$,

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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{2C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a23}, R^{c23}, and R^{d23} 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^{a23}, R^{c23} and R^{d23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c23} and R^{d23} 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^{b23} 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^{b23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

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}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)NR^{c3}(OR^{a3})$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$, 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, or 4 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, or 4 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, or 4 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, or 4 independently selected R^{3A} substituents;

each R^{3A} 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^{a31}, SR^{a31}, $C(O)R^{b31}$, $C(O)NR^{c31}R^{d31}$, $C(O)NR^{c31}(OR^{a31})$, $C(O)OR^{a31}$, $OC(O)R^{b31}$, $OC(O)NR^{c31}R^{d31}$, $NR^{c31}R^{d31}$, $NR^{c31}C(O)R^{b31}$, $NR^{c31}C(O)OR^{a31}$, $NR^{c31}C(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)R^{b31}$, $NR^{c31}S(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)_2R^{b31}$, $NR^{c31}S(O)_2NR^{c31}R^{d31}$, $S(O)R^{b31}$, $S(O)NR^{c31}R^{d31}$, $S(O)_2R^{b31}$, and $S(O)_2NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} 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, 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^{a31}, R^{c31} and R^{d31} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} 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 5-10 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, or 4 independently selected R^{3B} 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, 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^{b31} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{3B} 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^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, $C(O)NR^{c32}(OR^{a32})$, $C(O)OR^{a32}$, $OC(O)R^{b32}$, $OC(O)NR^{c32}R^{d32}$, $NR^{c32}R^{d32}$, $NR^{c32}C(O)R^{b32}$, $NR^{c32}C(O)OR^{a32}$, $NR^{c32}C(O)NR^{c32}R^{d32}$, $NR^{c32}S(O)R^{b32}$, $NR^{c32}S(O)NR^{c32}R^{d32}$, $NR^{c32}S(O)_2R^{b32}$, $NR^{c32}S(O)_2NR^{c32}R^{d32}$, $S(O)R^{b32}$, $S(O)NR^{c32}R^{d32}$, $S(O)_2R^{b32}$, and $S(O)_2NR^{c32}R^{d32}$, 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^{3B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3C} substituents;

each R^{a32}, R^{c32}, and R^{d32} 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^{a32}, R^{c32} and R^{d32} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3C} substituents;

or, any R^{c32} and R^{d32} 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, or 4 independently selected R^{3C} substituents;

each R^{b32} 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^{b32} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3C} substituents;

each R^{3C} 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^{a33}, SR^{a33}, $C(O)R^{b33}$, $C(O)NR^{c33}R^{d33}$, $C(O)NR^{c33}(OR^{a33})$, $C(O)OR^{a33}$, $OC(O)R^{b33}$, $OC(O)NR^{c33}R^{d33}$, $NR^{c33}R^{d33}$, $NR^{c33}C(O)R^{b33}$, $NR^{c33}C(O)OR^{a33}$, $NR^{c33}C(O)NR^{c33}R^{d33}$, $NR^{c33}S(O)R^{b33}$, $NR^{c33}S(O)NR^{c33}R^{d33}$, $NR^{c33}S(O)_2R^{b33}$, $NR^{c33}S(O)_2NR^{c33}R^{d33}$, $S(O)R^{b33}$, $S(O)NR^{c33}R^{d33}$, $S(O)_2R^{b33}$, and $S(O)_2NR^{c33}R^{d33}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{3C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{M} substituents;

each R^{a33}, R^{c33}, and R^{d33} 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^{a33}, R^{c33} and R^{d33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c33} and R^{d33} 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^{b33} 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^{b33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)NR^{c4}(OR^{a4})$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 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, or 4 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, or 4 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, or 4 independently selected R^{4A} substituents;

each R^{4A} 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^{a41}, SR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, $C(O)NR^{c41}(OR^{a41})$, $C(O)OR^{a41}$, $OC(O)R^{b41}$, $OC(O)NR^{c41}R^{d41}$, $NR^{c41}R^{d41}$, $NR^{c41}C(O)R^{b41}$, $NR^{c41}C(O)OR^{a41}$, $NR^{c41}C(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)R^{b41}$, $NR^{c41}S(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)_2R^{b41}$, $NR^{c41}S(O)_2NR^{c41}R^{d41}$, $S(O)R^{b41}$, $S(O)NR^{c41}R^{d41}$, $S(O)_2R^{b41}$, and $S(O)_2NR^{c41}R^{d41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} 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, 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^{a41}, R^{c41} and R^{d41} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} 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 5-10 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, or 4 independently selected R^{4B} 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, 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^{b41} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents;

each R^{4B} 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^{a42}, SR^{a42}, $C(O)R^{b42}$, $C(O)NR^{c42}R^{d42}$, $C(O)NR^{c42}(OR^{a42})$, $C(O)OR^{a42}$, $OC(O)R^{b42}$, $OC(O)NR^{c42}R^{d42}$, $NR^{c42}R^{d42}$, $NR^{c42}C(O)R^{b42}$, $NR^{c42}C(O)OR^{a42}$, $NR^{c42}C(O)NR^{c42}R^{d42}$, $NR^{c42}S(O)R^{b42}$, $NR^{c42}S(O)NR^{c42}R^{d42}$, $NR^{c42}S(O)_2R^{b42}$, $NR^{c42}S(O)_2NR^{c42}R^{d42}$, $S(O)R^{b42}$, $S(O)NR^{c42}R^{d42}$, $S(O)_2R^{b42}$, and $S(O)_2NR^{c42}R^{d42}$, 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^{4B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4C} substituents;

each R^{a42}, R^{c42}, and R^{d42} 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^{a42}, R^{c42} and R^{d42} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4C} substituents;

or, any R^{c42} and R^{d42} 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, or 4 independently selected R^{4C} substituents;

each R^{b42} 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^{b42} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4C} substituents;

each R^{4C} 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^{a43}, SR^{a43}, $C(O)R^{b43}$, $C(O)NR^{c43}R^{d43}$, $C(O)NR^{c43}(OR^{a43})$, $C(O)OR^{a43}$,

$OC(O)R^{b43}$, $OC(O)NR^{c43}R^{d43}$, $NR^{c43}R^{d43}$, $NR^{c43}C(O)R^{b43}$, $NR^{c43}C(O)OR^{a43}$, $NR^{c43}C(O)NR^{c43}R^{d43}$, $NR^{c43}S(O)R^{b43}$, $NR^{c43}S(O)NR^{c43}R^{d43}$, $NR^{c43}S(O)_2R^{b43}$, $NR^{c43}S(O)_2NR^{c43}R^{d43}$, $S(O)R^{b43}$, $S(O)NR^{c43}R^{d43}$, $S(O)_2R^{b43}$, and $S(O)_2NR^{c43}R^{d43}$, 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^{4C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a43}, R^{c43}, and R^{d43} 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^{a43}, R^{c43} and R^{d43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c43} and R^{d43} 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^{b43} 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^{b43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

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, 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-.

In some embodiments:

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

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

each R^{2A} is independently selected from D, 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^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, , 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^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} 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, 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^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} 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 5-10 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, or 4 independently selected R^{2B} 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, 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^{b21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

each R^{2B} is independently selected from D, 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^{a22}, SR^{a22}, $C(O)R^{b22}$, $C(O)NR^{c22}R^{d22}$, $C(O)NR^{c22}(OR^{a22})$, $C(O)OR^{a22}$, $OC(O)R^{b22}$, $OC(O)NR^{c22}R^{d22}$, $NR^{c22}R^{d22}$, $NR^{c22}C(O)R^{b22}$, $NR^{c22}C(O)OR^{a22}$, $NR^{c22}C(O)NR^{c22}R^{d22}$, $NR^{c22}S(O)R^{b22}$, $NR^{c22}S(O)NR^{c22}R^{d22}$, $NR^{c22}S(O)_2R^{b22}$, $NR^{c22}S(O)_2NR^{c22}R^{d22}$, $S(O)R^{b22}$, $S(O)NR^{c22}R^{d22}$, $S(O)_2R^{b22}$, and $S(O)_2NR^{c22}R^{d22}$, 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^{2B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2C} substituents;

each R^{a22}, R^{c22}, and R^{d22} 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^{a22}, R^{c22} and R^{d22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

or, any R^{c22} and R^{d22} 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, or 4 independently selected R^{2C} substituents;

each R^{b22} 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^{b22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{2C} is independently selected from D, 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^{a23}, SR^{a23}, $C(O)R^{b23}$, $C(O)NR^{c23}R^{d23}$, $C(O)NR^{c23}(OR^{a23})$, $C(O)OR^{a23}$, $OC(O)R^{b23}$, $OC(O)NR^{c23}R^{d23}$, $NR^{c23}R^{d23}$, $NR^{c23}C(O)R^{b23}$,

$NR^{c23}C(O)OR^{a23}$, $NR^{c23}C(O)NR^{c23}R^{d23}$, $NR^{c23}S(O)R^{b23}$, $NR^{c23}S(O)NR^{c23}R^{d23}$, $NR^{c23}S(O)_2R^{b23}$, $NR^{c23}S(O)_2NR^{c23}R^{d23}$, $S(O)R^{b23}$, $S(O)NR^{c23}R^{d23}$, $S(O)_2R^{b23}$, and $S(O)_2NR^{c23}R^{d23}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{2C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a23}, R^{c23}, and R^{d23} 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^{a23}, R^{c23} and R^{d23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c23} and R^{d23} 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^{b23} 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^{b23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

R^3 is selected from H, D, 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}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)NR^{c3}(OR^{a3})$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$, 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, or 4 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, or 4 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, or 4 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, or 4 independently selected R^{3A} substituents;

each R^{3A} is independently selected from D, 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^{a31}, SR^{a31}, $C(O)R^{b31}$, $C(O)NR^{c31}R^{d31}$, $C(O)NR^{c31}(OR^{a31})$, $C(O)OR^{a31}$, $OC(O)R^{b31}$, $OC(O)NR^{c31}R^{d31}$, $NR^{c31}R^{d31}$, $NR^{c31}C(O)R^{b31}$, $NR^{c31}C(O)OR^{a31}$, $NR^{c31}C(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)R^{b31}$, $NR^{c31}S(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)_2R^{b31}$, $NR^{c31}S(O)_2NR^{c31}R^{d31}$, $S(O)R^{b31}$, $S(O)NR^{c31}R^{d31}$, $S(O)_2R^{b31}$, and $S(O)_2NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} 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, 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^{a31}, R^{c31} and R^{d31} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} 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 5-10 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, or 4 independently selected R^{3B} 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, 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^{b31} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{3B} is independently selected from D, 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^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, $C(O)NR^{c32}(OR^{a32})$, $C(O)OR^{a32}$, $OC(O)R^{b32}$, $OC(O)NR^{c32}R^{d32}$, $NR^{c32}R^{d32}$, $NR^{c32}C(O)R^{b32}$, $NR^{c32}C(O)OR^{a32}$, $NR^{c32}C(O)NR^{c32}R^{d32}$, $NR^{c32}S(O)R^{b32}$, $NR^{c32}S(O)NR^{c32}R^{d32}$, $NR^{c32}S(O)_2R^{b32}$, $NR^{c32}S(O)_2NR^{c32}R^{d32}$, $S(O)R^{b32}$, $S(O)NR^{c32}R^{d32}$, $S(O)_2R^{b32}$, and $S(O)_2NR^{c32}R^{d32}$, 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^{3B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3C} substituents;

each R^{a32}, R^{c32}, and R^{d32} 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^{a32}, R^{c32} and R^{d32} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3C} substituents;

or, any R^{c32} and R^{d32} 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, or 4 independently selected R^{3C} substituents;

each R^{b32} 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^{b32} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3C} substituents;

each R^{3C} is independently selected from D, 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^{a33}, SR^{a33}, $C(O)R^{b33}$, $C(O)NR^{c33}R^{d33}$, $C(O)NR^{c33}(OR^{a33})$, $C(O)OR^{a33}$, $OC(O)R^{b33}$, $OC(O)NR^{c33}R^{d33}$, $NR^{c33}R^{d33}$, $NR^{c33}C(O)R^{b33}$, $NR^{c33}C(O)OR^{a33}$, $NR^{c33}C(O)NR^{c33}R^{d33}$, $NR^{c33}S(O)R^{b33}$, $NR^{c33}S(O)NR^{c33}R^{d33}$, $NR^{c33}S(O)_2R^{b33}$, $NR^{c33}S(O)_2NR^{c33}R^{d33}$, $S(O)R^{b33}$, $S(O)NR^{c33}R^{d33}$, $S(O)_2R^{b33}$, and $S(O)_2NR^{c33}R^{d33}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{3C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{M} substituents;

each R^{a33}, R^{c33}, and R^{d33} 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^{a33}, R^{c33} and R^{d33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c33} and R^{d33} 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^{b33} 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^{b33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)NR^{c4}(OR^{a4})$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 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, or 4 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, or 4 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, or 4 independently selected R^{4A} substituents;

each R^{4A} is independently selected from D, 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^{a41}, SR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, $C(O)NR^{c41}(OR^{a41})$, $C(O)OR^{a41}$, $OC(O)R^{b41}$, $OC(O)NR^{c41}R^{d41}$, $NR^{c41}R^{d41}$, $NR^{c41}C(O)R^{b41}$, $NR^{c41}C(O)OR^{a41}$, $NR^{c41}C(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)R^{b41}$, $NR^{c41}S(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)_2R^{b41}$, $NR^{c41}S(O)_2NR^{c41}R^{d41}$, $S(O)R^{b41}$, $S(O)NR^{c41}R^{d41}$, $S(O)_2R^{b41}$, and $S(O)_2NR^{c41}R^{d41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} 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, 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^{a41}, R^{c41} and R^{d41} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} 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 5-10 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, or 4 independently selected R^{4B} 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, 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^{b41} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents;

each R^{4B} is independently selected from D, 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^{a42}, SR^{a42}, $C(O)R^{b42}$, $C(O)NR^{c42}R^{d42}$, $C(O)NR^{c42}(OR^{a42})$, $C(O)OR^{a42}$, $OC(O)R^{b42}$, $OC(O)NR^{c42}R^{d42}$, $NR^{c42}R^{d42}$, $NR^{c42}C(O)R^{b42}$, $NR^{c42}C(O)OR^{a42}$, $NR^{c42}C(O)NR^{c42}R^{d42}$, $NR^{c42}S(O)R^{b42}$, $NR^{c42}S(O)NR^{c42}R^{d42}$, $NR^{c42}S(O)_2R^{b42}$, $NR^{c42}S(O)_2NR^{c42}R^{d42}$, $S(O)R^{b42}$, $S(O)NR^{c42}R^{d42}$, $S(O)_2R^{b42}$, and $S(O)_2NR^{c42}R^{d42}$, 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^{4B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4C} substituents;

each R^{a42}, R^{c42}, and R^{d42} 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^{a42}, R^{c42} and R^{d42} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4C} substituents;

or, any R^{c42} and R^{d42} 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, or 4 independently selected R^{4C} substituents;

each R^{b42} 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^{b42} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4C} substituents;

each R^{4C} is independently selected from D, 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^{a43}, SR^{a43}, $C(O)R^{b43}$, $C(O)NR^{c43}R^{d43}$, $C(O)NR^{c43}(OR^{a43})$,

$C(O)OR^{a43}$, $OC(O)R^{b43}$, $OC(O)NR^{c43}R^{d43}$, $NR^{c43}R^{d43}$, $NR^{c43}C(O)R^{b43}$, $NR^{c43}C(O)OR^{a43}$, $NR^{c43}C(O)NR^{c43}R^{d43}$, $NR^{c43}S(O)R^{b43}$, $NR^{c43}S(O)NR^{c43}R^{d43}$, $NR^{c43}S(O)_2R^{b43}$, $NR^{c43}S(O)_2NR^{c43}R^{d43}$, $S(O)R^{b43}$, $S(O)NR^{c43}R^{d43}$, $S(O)_2R^{b43}$, and $S(O)_2NR^{c43}R^{d43}$, 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^{4C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a43}, R^{c43}, and R^{d43} 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^{a43}, R^{c43} and R^{d43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c43} and R^{d43} 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^{b43} 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^{b43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^M is independently selected from H, D, 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, 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-.

In some embodiments, R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with 1, 2, 3, or 4 independently selected R^{1A} substituents.

In some embodiments, R^1 is selected from H, and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with 1, 2, or 3 independently selected R^{1A} substituents.

In some embodiments, each R^{1A} is independently selected from halo, CN, NO_2, OR^{a11}, and SR^{a11}.

In some embodiments, each R^{1A} is independently selected from D, halo, CN, NO_2, OR^{a11}, and SR^{a11}.

In some embodiments, each R^{a11} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{a11} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{1A} is independently selected from halo, CN, NO_2, OR^{a11}, and SR^{a11}, wherein each R^{a11} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{1A} is independently selected from D, halo, CN, NO_2, OR^{a11}, and SR^{a11}, wherein each R^{a11} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{1A} is OR^{a11}.

In some embodiments, each R^{1A} is OR^{a11}, wherein each R^{a11} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{1A} is OH.

In some embodiments, each R^{1A} is independently selected from halo, CN, NO_2, OR^{a11}, and SR^{a11}, wherein each R^{a11} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{1A} is independently selected from D, halo, CN, NO_2, OR^{a11}, and SR^{a11}, wherein each R^{a11} is independently selected from H and C_{1-6} alkyl.

In some embodiments, R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH.

In some embodiments, R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH; and wherein one or more hydrogen atoms of R^1 are optionally replaced by deuterium atoms.

In some embodiments, R^1 is selected from H, methyl, ethyl, and hydroxyethyl.

In some embodiments, R^1 is H.

In some embodiments, R^1 is methyl or ethyl.

In some embodiments, R^1 is methyl.

In some embodiments, R^1 is hydroxyethyl.

In some embodiments, R^2 is selected from H, 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-, 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^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents.

In some embodiments, R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (6-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (6-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents.

In some embodiments, R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6

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

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

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

In some embodiments, R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents.

In some embodiments, R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents.

In some embodiments, R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-

10 membered heteroaryl, 6-10 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1 or 2 independently selected R^{2A} substituents.

In some embodiments, R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl- of R^2 are each optionally substituted with 1 or 2 independently selected R^{2A} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, $OS(O)_2R^{b21}$, SF_5, $P(O)R^{f21}R^{g21}$, $OP(O)(OR^{h21})(OR^{i21})$, $P(O)(OR^{h21})(OR^{i21})$, and $BR^{j21}R^{k21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, $OS(O)_2R^{b21}$, SF_5, $P(O)R^{f21}R^{g21}$, $OP(O)(OR^{h21})(OR^{i21})$, $P(O)(OR^{h21})(OR^{i21})$, and $BR^{j21}R^{k21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, $OS(O)_2R^{b21}$, SF_5, $P(O)R^{f21}R^{g21}$, $OP(O)(OR^{h21})(OR^{i21})$, $P(O)(OR^{h21})(OR^{i21})$, and $BR^{j21}R^{k21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, $OS(O)_2R^{b21}$, SF_5, $P(O)R^{f21}R^{g21}$, $OP(O)(OR^{h21})(OR^{i21})$, $P(O)(OR^{h21})(OR^{i21})$, and $BR^{j21}R^{k21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21},

SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)OR^{a21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)OR^{a21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)OR^{a21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)OR^{a21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)_2R^{b21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)_2R^{b21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)_2R^{b21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} is optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, and $NR^{c21}C(O)R^{b21}$.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)_2R^{b21}$,

wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, OR^{a21}, and $C(O)NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)_2R^{b21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, OR^{a21}, and $C(O)NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1 or 2 independently selected R^{2B} substituents.

In some embodiments, each R^{2A} is independently selected from C_{1-6} alkyl, OR^{a21}, and $C(O)NR^{c21}R^{d21}$.

In some embodiments, 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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{a21}, R^{c21}, and R^{d21} is independently selected from H and C_{1-6} alkyl;

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

wherein each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, each R^{a21}, R^{b21}, 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, wherein the C_{1-6} alkyl,

C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{b21}, R^{c21}, and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

In some embodiments, 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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

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

In some embodiments, each R^{a21}, R^{b21}, R^{c21}, and R^{d21} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{a21}, R^{c21}, and R^{d21} is independently selected from H and C_{1-6} alkyl.

In some embodiments, any R^{c21} and R^{d21}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl.

In some embodiments, each R^{a21}, R^{b21}, 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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{b21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

In some embodiments, 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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

In some embodiments, each R^{a21}, R^{b21}, R^{c21}, and R^{d21} is independently selected from H and C_{1-6} alkyl;

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

In some embodiments, each R^{a21}, R^{c21}, and R^{d21} is independently selected from H and C_{1-6} alkyl;

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

In some embodiments, each R^{2B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{2B} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2C} substituents.

In some embodiments, each R^{2C} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2.

In some embodiments, each R^{2C} is CN.

In some embodiments, each R^{2B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2, wherein the C_{1-6} alkyl and C_{2-6} alkenyl are each optionally substituted by CN.

In some embodiments, each R^{2B} is CN or cyanomethyl.

In some embodiments, each R^{2B} is CN.

In some embodiments, each R^{2B} is cyanomethyl.

In some embodiments, each R^{2A} is independently selected from methyl, methoxy, cyclobutyl, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl, wherein the cyclobutyl of R^{2A} is optionally substituted by 1 or 2 R^{2B} substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2; and wherein each C_{1-6} alkyl of R^{2B} is optionally substituted by cyano.

In some embodiments, each R^{2A} is independently selected from methyl, methoxy, cyclobutyl, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl, wherein the cyclobutyl of R^{2A} is optionally substituted by C_{1-6} alkyl; and wherein the C_{1-6} alkyl of R^{2B} is optionally substituted by cyano.

In some embodiments, each R^{2A} is independently selected from methyl, methoxy, cyclobutyl, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino,

methylaminocarbonyl, and methylsulfonyl, wherein the cyclobutyl of R^{2A} is optionally substituted by cyanomethyl.

In some embodiments, each R^{2A} is independently selected from methyl, methoxy, cyanomethylcyclobutyl, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl.

In some embodiments, each R^{2A} is independently selected from methyl, methoxy, ethylamido, methoxyethylamido, and piperidinylcarbonyl.

In some embodiments, each R^{2A} is independently selected from methyl, methoxy, and piperidinylcarbonyl.

In some embodiments, R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups independently selected from methyl, cyclobutyl, methoxy, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl; wherein each cyclobutyl of R^{2A} is optionally substituted by one R^{2B} substituent which is $C_{1\text{-}6}$ alkyl, and wherein the $C_{1\text{-}6}$ alkyl of R^{2B} is optionally substituted by cyano.

In some embodiments, R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups independently selected from methyl, cyanomethylcyclobutyl, methoxy, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl,

methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl.

In some embodiments, R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups independently selected from methyl, methoxy, ethylamido, methoxyethylamido, and piperidinylcarbonyl.

In some embodiments, R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups independently selected from methyl, methoxy, and piperidinylcarbonyl.

In some embodiments, 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-, 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^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents.

In some embodiments, R^3 is selected from H, D, 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^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents.

In some embodiments, R^3 is selected from H, 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_{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, or 4 independently selected R^{3A} substituents.

In some embodiments, R^3 is selected from H, 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_{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, or 4 independently selected R^{3A} substituents.

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

In some embodiments, R^3 is selected from H, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents.

In some embodiments, R^3 is selected from H, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-6 membered heterocycloalkyl, wherein the phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-6 membered

heterocycloalkyl of R^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents.

In some embodiments, R^3 is selected from H, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, wherein the phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents.

In some embodiments, R^3 is selected from H, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-6 membered heterocycloalkyl, wherein the C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^3 are each optionally substituted with 1 or 2 independently selected R^{3A} substituents.

In some embodiments, R^3 is selected from H, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl, wherein the phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^3 are each optionally substituted with 1 or 2 independently selected R^{3A} substituents.

In some embodiments, each R^{3A} is independently selected from 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^{a31}, $C(O)R^{b31}$, SR^{a31}, SO_2R^{b31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from 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^{a31}, SR^{a31}, SO_2R^{b31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from 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^{a31}, $C(O)R^{b31}$, SR^{a31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from 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^{a31}, SR^{a31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from D, 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^{a31}, $C(O)R^{b31}$, SR^{a31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from D, 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^{a31}, SR^{a31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} 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-, CN, OR^{a31}, $C(O)R^{b31}$, and SO_2R^{b31}, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, and C_{6-10} aryl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, CN, OR^{a31}, and SO_2R^{b31}, wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, and C_{6-10} aryl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, $C(O)R^{b31}$, SO_2R^{b31}, and OR^{a31}, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents, and wherein each R^{a31} and R^{b31} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3A} is independently selected from methyl, trideuteromethyl, phenyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, methylcarbonyl, and methylsulfonyl, wherein the methyl group of the methylcarbonyl is substituted by methylsulfonylphenyl.In some embodiments, each R^{3A} is independently selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, SO_2R^{b31}, and OR^{a31}, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents, and wherein each R^{a31} and R^{b31} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3A} is independently selected from 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, $C(O)R^{b31}$, and OR^{a31}, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from 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^{a31}, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, CN, $C(O)R^{b31}$, and OR^{a31}, wherein the C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, and C_{6-10} aryl-C_{1-6} alkyl- of

R^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl-, CN, and OR^{a31}, wherein the C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, and C_{6-10} aryl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, $C(O)R^{b31}$, and OR^{a31}, wherein the C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents.

In some embodiments, each R^{3A} is independently selected from C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, and OR^{a31}, wherein the C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents.

In some embodiments, each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

In some embodiments, each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is optionally substituted with 1 or 2 independently selected R^{3B} substituents.

In some embodiments, each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is optionally substituted with 1 or 2 independently selected R^{3B} substituents.

In some embodiments, each R^{a31} and R^{b31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is optionally substituted with 1 or 2 independently selected R^{3B} substituents.

In some embodiments, each R^{a31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{a31} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{b31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of each R^{b31} is optionally substituted with 1 or 2 independently selected R^{3B} substituents.

In some embodiments, each R^{b31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^{b31} is optionally substituted with 1 or 2 independently selected R^{3B} substituents.

In some embodiments, each R^{b31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^{b31} is optionally substituted with phenyl, wherein the phenyl is optionally substituted with methylsulfonyl.

In some embodiments, each R^{b31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^{b31} is optionally substituted with methylsulfonylphenyl.

In some embodiments, each R^{3A} is independently selected from C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, $C(O)R^{b31}$, and OR^{a31}, wherein the C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents, wherein each R^{a31} is independently selected from H and C_{1-6} alkyl; and each R^{b31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^{b31} is optionally substituted with methylsulfonylphenyl.

In some embodiments, each R^{3A} is independently selected from C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, and OR^{a31}, wherein the C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents, wherein each R^{a31} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$, wherein each phenyl and 4-6 membered heterocycloalkyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$.

In some embodiments, each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$; and each R^{b33} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with methylsulfonyl.

In some embodiments, each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$.

In some embodiments, each R^{3B} is independently selected from phenyl, 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$;

each R^{a32} is independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl;

each R^{b32} is independently selected from H and C_{1-6} alkyl; and

and each R^{b33} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3B} is independently selected from phenyl, 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with methylsulfonyl;

each R^{a32} is independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl;

each R^{b32} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3B} is independently selected from 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$, wherein each R^{a32} is

independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl; and wherein each R^{b32} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with methylsulfonyl.

In some embodiments, each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$.

In some embodiments, each R^{3B} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$.

In some embodiments, each R^{3B} is independently selected from phenyl, CN and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with methylsulfonyl.

In some embodiments, each R^{3B} is independently selected from CN and $C(O)OR^{a32}$.

In some embodiments, wherein each R^{a32} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, wherein each R^{a32} is independently selected from H and C_{1-6} alkyl.

In some embodiments, wherein each R^{a32} is H.

In some embodiments, each R^{3B} is independently selected from CN and $C(O)OR^{a32}$, wherein each R^{a32} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{3B} is independently selected from phenyl, morpholinyl, CN, tetrahydropyranyloxy, methylcarbonyl, and C(O)OH.

In some embodiments, each R^{3B} is independently selected from morpholinyl, CN, tetrahydropyranyloxy, methylcarbonyl, and C(O)OH.

In some embodiments, each R^{3B} is independently selected from CN and C(O)OH.

In some embodiments, each R^{3A} is independently selected from methyl, trideuteromethyl, phenyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl,

morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, methylcarbonyl, and methylsulfonyl, wherein the methyl group of the methylcarbonyl is substituted by methylsulfonylphenyl.

In some embodiments, R^3 is selected from H, ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl, wherein the ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl are each optionally substituted by one or two R^{3A} groups independently selected from methyl, trideuteromethyl, phenyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, methylcarbonyl, and methylsulfonyl, wherein the methyl group of the methylcarbonyl is substituted by methylsulfonylphenyl.

In some embodiments, R^3 is selected from H, ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl, wherein the ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl are each optionally substituted by one or two R^{3A} groups independently selected from methyl, trideuteromethyl, phenyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, (methylsulfonylphenyl)methylcarbonyl, and methylsulfonyl.

In some embodiments, R^3 is selected from H, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, and pyridyl, wherein the phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, and pyridyl are each optionally substituted by one or two R^{3A} groups independently selected from methyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, and methylsulfonyl.

In some embodiments, R^3 is selected from H, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, and pyridyl, wherein the phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, and pyridyl are each optionally substituted by one or two R^{3A} groups independently selected from cyano, methoxy, cyclopropyl, cyanocyclopropyl, benzyl, and carboxybenzyl.

In some embodiments, R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$,

$S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from halo, C_{2-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the C_{2-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from halo, C_{2-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the C_{2-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered

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

In some embodiments, R^4 is selected from C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl,

phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl-, of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, R^4 is selected from C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{2-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

In some embodiments, each R^{a4}, R^{b4}, 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_{3-6} cycloalkyl, and phenyl.

In some embodiments, each R^{a4}, R^{b4}, 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, and C_{3-6} cycloalkyl.

In some embodiments, each R^{a4} and R^{b4} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{a4} and R^{b4} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{b4} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{b4} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{b4} is H.

In some embodiments, each R^{b4} is C_{1-6} alkyl.

In some embodiments, each 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, and C_{3-6} cycloalkyl.

In some embodiments, each R^{c4} and R^{d4} is independently selected from H, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

In some embodiments, each R^{c4} and R^{d4} is independently selected from H and C_{3-6} cycloalkyl.

In some embodiments, each R^{c4} and R^{d4} is independently selected from H and cyclopropyl.

In some embodiments, R^{c4} is H and R^{d4} is independently selected from H and C_{3-6} cycloalkyl.

In some embodiments, R^{c4} is H and R^{d4} is independently selected from H and cyclopropyl.

In some embodiments, R^{c4} is H and R^{d4} is cyclopropyl.

In some embodiments, each R^{4A} is independently selected from 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, OR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents.

In some embodiments, each R^{4A} is independently selected from 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-, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents.

In some embodiments, each R^{4A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents; wherein each R^{a41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl; and wherein each R^{b41} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, and $C(O)R^{b41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents; wherein each R^{a41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl; and wherein each R^{b41} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4A} is independently selected from halo, C_{1-6} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$ wherein the C_{1-6} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents.

In some embodiments, each R^{4A} is independently selected from halo, C_{1-6} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-6} alkyl-, and $C(O)R^{b41}$, wherein the C_{1-6} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents.

In some embodiments, each R^{a41}, R^{b41}, 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, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl.

In some embodiments, each R^{a41}, R^{b41}, R^{c41}, and R^{d41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl.

In some embodiments, each R^{a41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl.

In some embodiments, each R^{b41} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{b41} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{b41} is H.

In some embodiments, each R^{b41} is C_{1-6} alkyl.

In some embodiments, each R^{c41} and R^{d41} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{c41} is H.

In some embodiments, each R^{c41} is C_{1-6} alkyl.

In some embodiments, each R^{d41} is H.

In some embodiments, each R^{d41} is C_{1-6} alkyl.

In some embodiments:

each R^{4A} is independently selected from halo, C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents; and

each R^{a41}, R^{b41}, 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, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl.

In some embodiments:

each R^{4A} is independently selected from halo, C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents; and

each R^{a41} and R^{b41} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl; and

each 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, and C_{3-6} cycloalkyl.

In some embodiments:

each R^{4A} is independently selected from halo, C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents; and

each R^{a41} and R^{b41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl; and

each R^{c41} and R^{d41} is independently selected from H and C_{3-6} cycloalkyl.

In some embodiments, each R^{4A} is independently selected from halo, C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, and $C(O)R^{b41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents; and wherein each R^{b41} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, cyano, hydroxy, methoxy, N,N-dimethylaminocarbonyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl, wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl, wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents.

In some embodiments, each R^{4B} is independently selected from C_{1-6} alkyl, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, cyano, hydroxy, methoxy, N,N-dimethylaminocarbonyl, ethyl, 2-methylpropyl, difluoroethyl, hydroxy, cyano, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, ethyl, 2-methylpropyl, difluoroethyl, hydroxy, cyano, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments, each R^{a42}, R^{b42}, R^{c42}, and R^{d42} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments, each R^{a42}, R^{b42}, R^{c42}, and R^{d42} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{a42}, R^{b42}, R^{c42}, and R^{d42} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{a42} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

In some embodiments, each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl, and wherein each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, ethyl, 2-methylpropyl, difluoroethyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide,

isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl, and wherein each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, ethyl, 2-methylpropyl, difluoroethyl, hydroxy, cyano, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl, and wherein each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl, wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments, each R^{4A} is independently selected from fluoro, methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl, wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6}

alkyl, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments, R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents.

In some embodiments, R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents.

In some embodiments, R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl;

wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents.

In some embodiments, R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and

pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl;

wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents.

In some embodiments, R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl;

wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl, wherein each R^{a42} is independently selected from H, and C_{1-6} alkyl.

In some embodiments, R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl,

cyclohexenyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl;

wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl, wherein each R^{a42} is independently selected from H, and C_{1-6} alkyl.

In some embodiments, R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl, of R^4 are optionally substituted by 1 or 2 R^{4A} substituents.

In some embodiments, R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents.

In some embodiments, R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from fluoro,

methyl, piperidinyl, piperazinyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl;

wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents.

In some embodiments, R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from fluoro, methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl;

wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents.

In some embodiments, R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from fluoro, methyl, piperidinyl, piperazinyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl;

wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments, R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from fluoro, methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl;

wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments:

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

R^2 is selected from H, 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-, 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^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, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

each R^{2B} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2, wherein each C_{1-6} alkyl of R^{2B} is optionally substituted by cyano;

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

each R^{3A} is independently selected from 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^{a31}, SR^{a31}, SO_2R^{b31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$, wherein each phenyl and 4-6 membered heterocycloalkyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents;

each R^{4A} is independently selected from 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, OR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents;

each R^{a41}, R^{b41}, 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, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

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

R^2 is selected from H, 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-, 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^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, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{3A} is independently selected from 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^{a31}, SR^{a31}, SO_2R^{b31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents; and

each R^{4A} is independently selected from 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, OR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents.

In some embodiments:

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

R^2 is selected from H, 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-, 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^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, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{3A} is independently selected from 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^{a31}, SR^{a31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents; and

each R^{4A} is independently selected from 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-,

$C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents.

In some embodiments:

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

R^2 is selected from H, 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-, 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^2 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2A} substituents;

each R^{2A} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

R^3 is selected from H, D, 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^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents;

each R^{3A} is independently selected from D, 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^{a31}, SR^{a31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{3B} is independently selected from D, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents; and

each R^{4A} is independently selected from 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-, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents.

In some embodiments:

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (6-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (6-10 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 C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)_2R^{b21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1 or 2 independently selected R^{2B} 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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein each C_{1-6} alkyl of R^{b21} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

each R^{2B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2, wherein each C_{1-6} alkyl of R^{2B} is optionally substituted by cyano;

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

each R^{3A} is independently selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, $C(O)R^{b31}$, SO_2R^{b31}, and OR^{a31}, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6

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

each R^{a31} and R^{b31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of each R^{a31} and R^{b31} is optionally substituted with 1 or 2 independently selected R^{3B} substituents;

each R^{3B} is independently selected from phenyl, 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$;

each R^{a32} is independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl;

each R^{b32} is independently selected from H and C_{1-6} alkyl;

R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents;

each R^{b4}, 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, and C_{3-6} cycloalkyl;

each R^{4A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents;

each R^{a41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^{b41} is independently selected from H and C_{1-6} alkyl;

each R^{c41} and R^{d41} is independently selected from H and C_{3-6} cycloalkyl;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-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 C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, and $NR^{c21}C(O)R^{b21}$;

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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{3A} is independently selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, OR^{a31}, and SO_2R^{b31}, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents;

each R^{a31} is independently selected from H and C_{1-6} alkyl;

each R^{b31} is independently selected from H and C_{1-6} alkyl;

each R^{3B} is independently selected from 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$;

each R^{a32} is independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl;

each R^{b32} is independently selected from H and C_{1-6} alkyl;

R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents;

each R^{4A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, and $C(O)R^{b41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents;

each R^{a41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^{b41} is independently selected from H and C_{1-6} alkyl;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6

membered heterocycloalkyl, and (5-6 membered heteroaryl)-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 C_{1-6} alkyl, OR^{a21}, and $C(O)NR^{c21}R^{d21}$;

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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

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

each R^{3A} is independently selected from C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, and OR^{a31}, wherein the C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents;

each R^{a31} is independently selected from H and C_{1-6} alkyl

each R^{3B} is independently selected from CN and $C(O)OR^{a32}$;

each R^{a32} is independently selected from H and C_{1-6} alkyl;

R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents;

each R^{4A} is independently selected from halo, C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, and $C(O)R^{b41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents;

each R^{b41} is independently selected from H and C_{1-6} alkyl;

each R^{4B} is independently selected from C_{1-6} alkyl, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

In some embodiments:

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups;

each R^{2A} is independently selected from methyl, cyclobutyl, methoxy, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl, wherein each cyclobutyl of R^{2A} is optionally substituted by one R^{2B} substituent which is C_{1-6} alkyl, and wherein the C_{1-6} alkyl of R^{2B} is optionally substituted by cyano;

R^3 is selected from H, ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl, wherein the ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl are each optionally substituted by one or two R^{3A} groups;

each R^{3A} is independently selected from methyl, trideuteromethyl, phenyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, methylcarbonyl, and

methylsulfonyl, wherein the methyl group of the methylcarbonyl is substituted by methylsulfonylphenyl;

R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents;

each R^{4A} is independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups;

each R^{2A} is independently selected from methyl, methoxy, ethylamido, methoxyethylamido, and piperidinylcarbonyl;

R^3 is selected from H, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazoyl, indazolyl, and pyridyl, wherein the phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, and pyridyl are each optionally substituted by one or two R^{3A} groups;

each R^{3A} is independently selected from methyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, and methylsulfonyl;

R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents;

each R^{4A} is independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups;

each R^{2A} is independently selected from methyl, methoxy, and piperidinylcarbonyl;

R^3 is selected from H, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, and pyridyl, wherein the phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, and pyridyl are each optionally substituted by one or two R^{3A} groups;

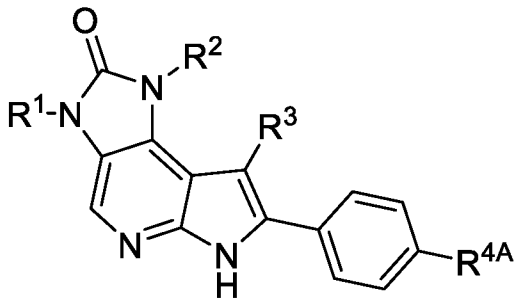
each R^{3A} is independently selected from cyano, methoxy, cyclopropyl, cyanocyclopropyl, benzyl, and carboxybenzyl;

R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents;

each R^{4A} is independently selected from fluoro, methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, and pyridylmethyl, wherein the methyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents; and

each R^{4B} is independently selected from C_{1-6} alkyl, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

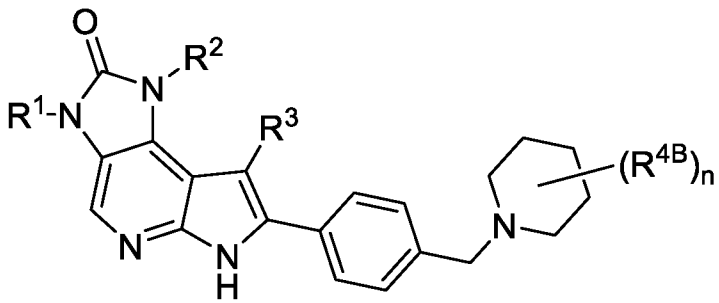
In some embodiments, the compound of Formula I is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein variables R^1, R^2, R^3, and R^{4A} are defined according to the definitions provided herein for compounds of Formula I.

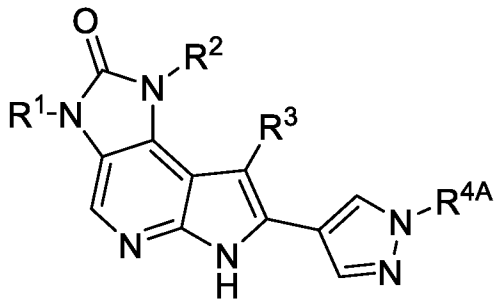
In some embodiments, the compound of Formula I is a compound of Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, 2, 3, or 4; and variables R^1, R^2, R^3, and R^{4B} are defined according to the definitions provided herein for compounds of Formula I.

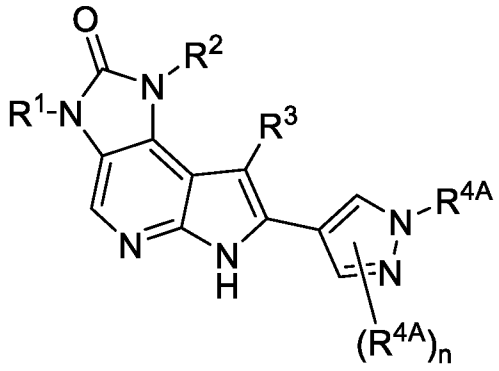
In some embodiments, the compound of Formula I is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein variables R^1, R^2, R^3, and R^{4A} are defined according to the definitions provided herein for compounds of Formula I.

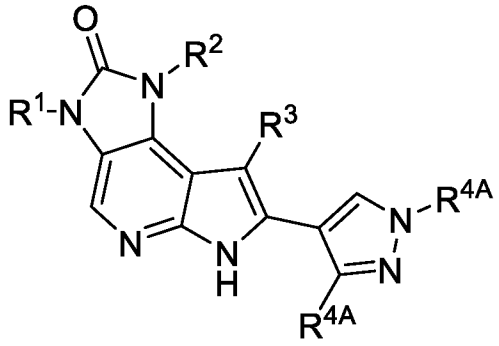
In some embodiments, the compound of Formula I is a compound of Formula IV:



IV

or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, or 2; and variables R^1, R^2, R^3, and R^{4A} are defined according to the definitions provided herein for compounds of Formula I.

In some embodiments, the compound of Formula I is a compound of Formula V:



V

or a pharmaceutically acceptable salt thereof, wherein variables R^1, R^2, R^3, and R^{4A} are defined according to the definitions provided herein for compounds of Formula I.

In some embodiments, the compound provided herein is selected from:

3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(benzofuran-5-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-(2-hydroxyethyl)-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-1H-pyrazol-4-yl)-3-methyl-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-methyl-7-(4-((methyl(3-(methylsulfonyl)propyl)amino)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(3-fluoro-4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3-methyl-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-(4-ethylpiperazin-1-yl)phenyl)-3-methyl-1-(pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclohexyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(tert-butyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclohexyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-ethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-methyl-7-(1-methyl-1H-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-(tetrahydro-2H-pyran-3-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-(4-ethylpiperazin-1-yl)phenyl)-3-methyl-1-((1-methyl-1H-pyrazol-4-yl)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-(4-ethylpiperazin-1-yl)phenyl)-3-methyl-1-(2-oxo-2-(piperidin-1-yl)ethyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclohexyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-isobutyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclobutyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(tert-butyl)-8-(4-methoxycyclohex-1-en-1-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

4-(1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

1-(4-(1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

4-((4-(1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)-1H-pyrazol-1-yl)methyl)benzoic acid;

1-cyclopentyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclopentyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(4-(1-cyclopentyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

1-(4-(1-cyclopentyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

1-cyclopentyl-8-(4-methoxycyclohex-1-en-1-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclopentyl-8-(3,6-dihydro-2H-pyran-4-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-cyclopropyl-1,3-dimethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(6-methoxypyridin-3-yl)-1,3-dimethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

4-(1-isopropyl-3-methyl-2-oxo-7-(1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

4-(7-(4-(4-acetylpiperazin-1-yl)phenyl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

4-(7-(3,6-dihydro-2H-pyran-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

4-(7-(3,6-dihydro-2H-pyran-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

1,3-dimethyl-8-phenyl-7-(pyridin-3-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1,3-dimethyl-8-phenyl-7-(piperidin-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(2-hydroxyethyl)-1,3-dimethyl-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-isobutyryl-1,3-dimethyl-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-isopropyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-(bicyclo[2.2.1]heptan-2-yl)-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one; and

3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-(4-(3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

1-(4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(4-(1-morpholinocyclopropyl)phenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-

(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(1-(2,2-difluoroethyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(thieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

(*S*)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-1-(tetrahydro-2*H*-pyran-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-8-(4-methoxyphenyl)-3-methyl-7-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyridin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-isopropyl-7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(6-isopropoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(6-((tetrahydro-2*H*-pyran-4-yl)oxy)pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(6-(pyridin-3-yloxy)pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-cyclopropyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(cyclohex-1-en-1-yl)-1-cyclopentyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one;

1-cyclopentyl-7-(2-hydroxyethyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-cyclopropyl-3-methyl-8-(thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-b]pyridin-2(1*H*)-one;

2-(1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)cyclopropane-1-carbonitrile;

N-(4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)-2-methoxyacetamide;

N-(4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2*H*)-yl)cyclohexyl)acetamide;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(2-morpholinothiazol-5-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-8-(isoquinolin-6-yl)-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(benzo[d]thiazol-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(chroman-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(6-(piperazin-1-yl)thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(6-(4-acetylpiperazin-1-yl)thieno[3,2-c]pyridin-2-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-

d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(5-(methylsulfonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(3-methylpyrrolo[1,2-a]pyrazin-7-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-8-(imidazo[1,5-a]pyridin-7-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(1-hydroxy-2,3-dihydro-1H-inden-5-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(3-azabicyclo[4.1.0]heptan-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

4-(1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)-N,N-dimethylbenzamide;

3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyrazolo[1,5-*a*]pyrimidin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one;

7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-

b]pyridin-2(1*H*)-one;

methyl (1*S*)-3-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate;

(1*S*)-3-(7-(4-methoxyphenyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;

7-(cyclopropyl(hydroxy)methyl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

4-((1-isopropyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)methyl)benzonitrile;

1-cyclopentyl-7-ethyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-N-cyclopropyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxamide;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(methylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-isopropyl-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-8-(phenylethynyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-b]pyridin-2(1*H*)-one;

2-((1*S*,3*S*)-3-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)acetonitrile;

2-((1*S*,4*S*)-4-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile;

2-((1*S*,4*S*)-4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile;

methyl ((1*S*,3*S*)-3-(3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2H)-yl)cyclobutyl)carbamate;

ethyl ((1*S*,3*S*)-3-(8-(4-cyanophenyl)-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate;

ethyl ((1*S*,3*S*)-3-(8-(4-methoxyphenyl)-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate;

1-isopropyl-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-8-(1-(2-(4-(methylsulfonyl)phenyl)acetyl)piperidin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

2-((1*S*,4*S*)-4-(7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile;

7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

3-methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-7-(pyrazolo[1,5-a]pyrimidin-3-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

2-(1-(4-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)piperidin-1-yl)cyclobutyl)acetonitrile; and

4-(3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-1-(2-(methylsulfonyl)-2-azaspiro[3.5]nonan-7-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile;

or a pharmaceutically acceptable salt thereof.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, divalent linking substituents are described. It is specifically intended that each divalent linking substituent include both

the forward and backward forms of the linking substituent. For example, -NR(CR'R'')$_n$- includes both -NR(CR'R'')$_n$- and -(CR'R'')$_n$NR-. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the phrase "optionally substituted" means unsubstituted or substituted. The substituents are independently selected, and substitution may be at any chemically accessible position. As used herein, the term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms. It is to be understood that substitution at a given atom is limited by valency.

As used herein, the phrase "each 'variable' is independently selected from" means substantially the same as wherein "at each occurrence 'variable' is selected from."

Throughout the definitions, the term "C_{n-m}" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-3}, C_{1-4}, C_{1-6}, and the like.

As used herein, the term "C_{n-m} alkyl", employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbons. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl (Me), ethyl (Et), *n*-propyl (*n*-Pr), isopropyl (iPr), *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms.

As used herein, "C_{n-m} alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds and having n to m carbons. Example alkenyl groups

include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, "C_{n-m} alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds and having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkoxy", employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n to m carbons. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), butoxy (e.g., *n*-butoxy and *tert*-butoxy), and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "amino" refers to a group of formula $-NH_2$.

As used herein, the term "aryl," employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings). The term "C_{n-m} aryl" refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 5 to 10 carbon atoms. In some embodiments, the aryl group is phenyl or naphthyl. In some embodiments, the aryl is phenyl.

As used herein, "halo" refers to F, Cl, Br, or I. In some embodiments, a halo is F, Cl, or Br. In some embodiments, a halo is F or Cl. In some embodiments, a halo is F. In some embodiments, a halo is Cl.

As used herein, "C_{n-m} haloalkoxy" refers to a group of formula –O-haloalkyl having n to m carbon atoms. Example haloalkoxy groups include OCF_3 and $OCHF_2$. In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} haloalkyl", employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms which may be the same or different, where "s" is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some

embodiments, the haloalkyl group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CH_2F, CCl_3, $CHCl_2$, C_2Cl_5 and the like.

As used herein, the term "carbonyl", employed alone or in combination with other terms, refers to a -C(O)- group.

As used herein, the term "C_{n-m} alkylcarbonyl" refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfonyl" refers to a group of formula -$S(O)_2$-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "carboxy" refers to a group of formula -C(O)OH.

As used herein, the term "di(C_{n-m} alkyl)amino" refers to a group of formula -$N(alkyl)_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl and alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2 fused rings) groups, spirocycles, and bridged rings (*e.g.*, a bridged bicycloalkyl group). Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido (e.g., C(O) or C(S)). Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, or 10 ring-forming carbons (i.e., C_{3-10}). In some embodiments, the cycloalkyl is a C_{3-10} monocyclic or bicyclic cycloalkyl. In some embodiments, the cycloalkyl is a C_{3-7} monocyclic cycloalkyl. In some embodiments, the cycloalkyl is a C_{4-7} monocyclic cycloalkyl. In some embodiments, the cycloalkyl is a C_{4-10} spirocycle or bridged cycloalkyl (*e.g.*, a bridged bicycloalkyl group). Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl,

cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, cubane, adamantane, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, spiro[3.3]heptanyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, "heteroaryl" refers to a monocyclic or polycyclic (e.g., having 2 fused rings) aromatic heterocycle having at least one heteroatom ring member selected from N, O, S and B. In some embodiments, the heteroaryl ring has 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, S and B. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl is a 5-10 membered monocyclic or bicyclic heteroaryl having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, S, and B. In some embodiments, the heteroaryl is a 5-10 membered monocyclic or bicyclic heteroaryl having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S. In some embodiments, the heteroaryl is a 5-6 monocyclic heteroaryl having 1 or 2 heteroatom ring members independently selected from N, O, S, and B. In some embodiments, the heteroaryl is a 5-6 monocyclic heteroaryl having 1 or 2 heteroatom ring members independently selected from N, O, and S. In some embodiments, the heteroaryl group contains 3 to 10, 4 to 10, 5 to 10, 5 to 7, 3 to 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to 4 ring-forming heteroatoms, 1 to 3 ring-forming heteroatoms, 1 to 2 ring-forming heteroatoms or 1 ring-forming heteroatom. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. Example heteroaryl groups include, but are not limited to, thienyl (or thiophenyl), furyl (or furanyl), pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, 1,3,4-oxadiazolyl and 1,2-dihydro-1,2-azaborine, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, azolyl, triazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1, 2-b]thiazolyl, purinyl, triazinyl, thieno[3,2-b]pyridinyl, imidazo[1,2-a]pyridinyl, 1,5-naphthyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, triazolo[4,3-a]pyridinyl, 1H-pyrrolo[3,2-b]pyridinyl, 1H-

pyrrolo[2,3-b]pyridinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, indazolyl, and the like.

As used herein, "heterocycloalkyl" refers to monocyclic or polycyclic heterocycles having at least one non-aromatic ring (saturated or partially unsaturated ring), wherein one or more of the ring-forming carbon atoms of the heterocycloalkyl is replaced by a heteroatom selected from N, O, S, and B, and wherein the ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by one or more oxo or sulfido (e.g., C(O), S(O), C(S), or $S(O)_2$, etc.). When a ring-forming carbon atom or heteroatom of a heterocycloalkyl group is optionally substituted by one or more oxo or sulfide, the O or S of said group is *in addition* to the number of ring-forming atoms specified herein (e.g., a 1-methyl-6-oxo-1,6-dihydropyridazin-3-yl is a 6-membered heterocycloalkyl group, wherein a ring-forming carbon atom is substituted with an oxo group, and wherein the 6-membered heterocycloalkyl group is further substituted with a methyl group). Heterocycloalkyl groups include monocyclic and polycyclic (e.g., having 2 fused rings) systems. Included in heterocycloalkyl are monocyclic and polycyclic 3 to 10, 4 to 10, 5 to 10, 4 to 7, 5 to 7, or 5 to 6 membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles and bridged rings (*e.g.*, a 5 to 10 membered bridged biheterocycloalkyl ring having one or more of the ring-forming carbon atoms replaced by a heteroatom independently selected from N, O, S, and B). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds.

Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the non-aromatic heterocyclic ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl group contains 3 to 10 ring-forming atoms, 4 to 10 ring-forming atoms, 3 to 7 ring-forming atoms, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to 4

heteroatoms, 1 to 3 heteroatoms, 1 to 2 heteroatoms or 1 heteroatom. In some embodiments, the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from N, O, S and B and having one or more oxidized ring members. In some embodiments, the heterocycloalkyl is a monocyclic or bicyclic 5-10 membered heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from N, O, S, and B and having one or more oxidized ring members. In some embodiments, the heterocycloalkyl is a monocyclic or bicyclic 5 to 10 membered heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and having one or more oxidized ring members. In some embodiments, the heterocycloalkyl is a monocyclic 5 to 6 membered heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and having one or more oxidized ring members.

Example heterocycloalkyl groups include pyrrolidin-2-one (or 2-oxopyrrolidinyl), 1,3-isoxazolidin-2-one, pyranyl, tetrahydropyranyl, oxetanyl, azetidinyl, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, 1,2,3,4-tetrahydroisoquinoline, benzazapene, azabicyclo[3.1.0]hexanyl, diazabicyclo[3.1.0]hexanyl, oxobicyclo[2.1.1]hexanyl, azabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.1]heptanyl, azabicyclo[3.1.1]heptanyl, diazabicyclo[3.1.1]heptanyl, azabicyclo[3.2.1]octanyl, diazabicyclo[3.2.1]octanyl, oxobicyclo[2.2.2]octanyl, azabicyclo[2.2.2]octanyl, azaadamantanyl, diazaadamantanyl, oxo-adamantanyl, azaspiro[3.3]heptanyl, diazaspiro[3.3]heptanyl, oxo-azaspiro[3.3]heptanyl, azaspiro[3.4]octanyl, diazaspiro[3.4]octanyl, oxo-azaspiro[3.4]octanyl, azaspiro[2.5]octanyl, diazaspiro[2.5]octanyl, azaspiro[4.4]nonanyl, diazaspiro[4.4]nonanyl, oxo-azaspiro[4.4]nonanyl, azaspiro[4.5]decanyl, diazaspiro[4.5]decanyl, diazaspiro[4.4]nonanyl, oxo-diazaspiro[4.4]nonanyl, oxo-dihydropyridazinyl, oxo-2,6-diazaspiro[3.4]octanyl, oxohexahydropyrrolo[1,2-a]pyrazinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 3-oxopiperazinyl, oxo-pyrrolidinyl, oxo-pyridinyl and the like.

As used herein, "C_{o-p} cycloalkyl-C_{n-m} alkyl-" refers to a group of formula cycloalkyl-alkylene-, wherein the cycloalkyl has o to p carbon atoms and the alkylene linking group has n to m carbon atoms.

As used herein "C_{o-p} aryl-C_{n-m} alkyl-" refers to a group of formula aryl-alkylene-, wherein the aryl has o to p carbon atoms and the alkylene linking group has n to m carbon atoms.

As used herein, "heteroaryl-C_{n-m} alkyl-" refers to a group of formula heteroaryl-alkylene-, wherein alkylene linking group has n to m carbon atoms.

As used herein "heterocycloalkyl-C_{n-m} alkyl-" refers to a group of formula heterocycloalkyl-alkylene-, wherein alkylene linking group has n to m carbon atoms.

As used herein, an "alkyl linking group" is a bivalent straight chain or branched alkyl linking group ("alkylene group"). For example, "C_{o-p} cycloalkyl-C_{n-m} alkyl-", "C_{o-p} aryl-C_{n-m} alkyl-", "phenyl-C_{n-m} alkyl-", "heteroaryl-C_{n-m} alkyl-", and "heterocycloalkyl-C_{n-m} alkyl-" contain alkyl linking groups. Examples of "alkyl linking groups" or "alkylene groups" include methylene, ethan-1,1-diyl, ethan-1,2-diyl, propan-1,3-dilyl, propan-1,2-diyl, propan-1,1-diyl and the like.

At certain places, the definitions or embodiments refer to specific rings (e.g., an azetidine ring, a pyridine ring, etc.). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring may be attached at any position of the ring, whereas a pyridin-3-yl ring is attached at the 3-position.

As used herein, the term "oxo" refers to an oxygen atom (i.e., =O) as a divalent substituent, forming a carbonyl group when attached to a carbon (e.g., C=O or C(O)), or attached to a nitrogen or sulfur heteroatom forming a nitroso, sulfinyl, or sulfonyl group.

As used herein, the term "independently selected from" means that each occurrence of a variable or substituent (*e.g.*, each R^M), are independently selected at each occurrence from the applicable list.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic

forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms. In some embodiments, the compound has the *(R)*-configuration. In some embodiments, the compound has the *(S)*-configuration. The Formulas (*e.g.*, Formula I, Formula Ia, etc.) provided herein include stereoisomers of the compounds.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds provided herein also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H-

isoindole, 2-hydroxypyridine and 2-pyridone, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

In some embodiments, preparation of compounds can involve the addition of acids or bases to affect, for example, catalysis of a desired reaction or formation of salt forms such as acid addition salts.

In some embodiments, the compounds provided herein, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds provided herein. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds provided herein, or salt thereof.

The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present application also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues

such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

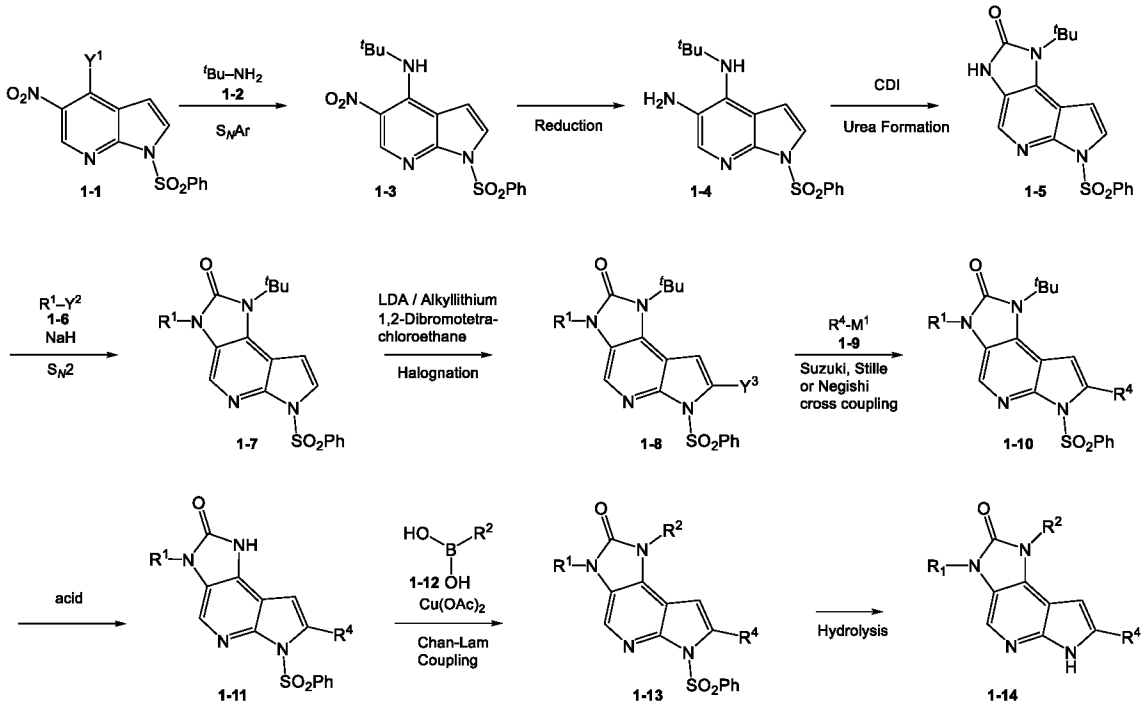
Synthesis

As will be appreciated by those skilled in the art, the compounds provided herein, including salts and stereoisomers thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

Compounds of Formula I provided herein can be prepared as shown in **Scheme 1** (*e.g.*, compounds of formula **1-14** in **Scheme 1**). Suitable starting materials **1-1**, where Y^1 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs), can be converted to amine **1-3** under standard conditions, such as S_NAr or Buchwald conditions (*e.g.*, in the presence of *tert*-butyl amine **1-2**). Reduction of the nitro group of **1-3** under standard conditions *(e.g.*, in the presence of Fe, H_2O and NH_4Cl) affords diamine **1-4**. Diamine **1-4** can be converted to cyclic urea **1-5** under standard conditions (*e.g.*, in the presence of CDI). Cyclic urea **1-5** can be further substituted to the tetrasubstituted urea **1-7** under standard conditions, such as S_N2 or Buchwald conditions (*e.g.*, in the presence of NaH and halide **1-6**, where Y^2 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs)). Urea **1-7** can be coverted to halide **1-8**, where Y^3 is a halogen (*e.g.*, Cl, Br, or I), under standard conditions (*e.g.*, in the presence of LDA or alkyllithium, 1,2-dibromotetrachloroethane in the case of

bromination). Halide **1-8** can be coupled with substituted metal **1-9** (*e.g.*, M^1 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (e.g., a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **1-10**. The *tert*-buty group of compound **1-10** can be removed under acidic conditions (*e.g.*, in the presence of TFA) to afford compound **1-11**. Compound **1-11** can be coupled with boronic acid **1-12**, where R^2 is a substituted or unsubstituted aryl or heteroaryl group, under standard Chan-Lam coupling condition (*e.g.*, in the presence of $Cu(OAc)_2$, diisopropylethylamine) to afford compound **1-13**. Deprotection of compound **1-13** under standard hydrolysis conditions (*e.g.*, in the presence of water and sodium hydroxide) affords compound **1-14**.

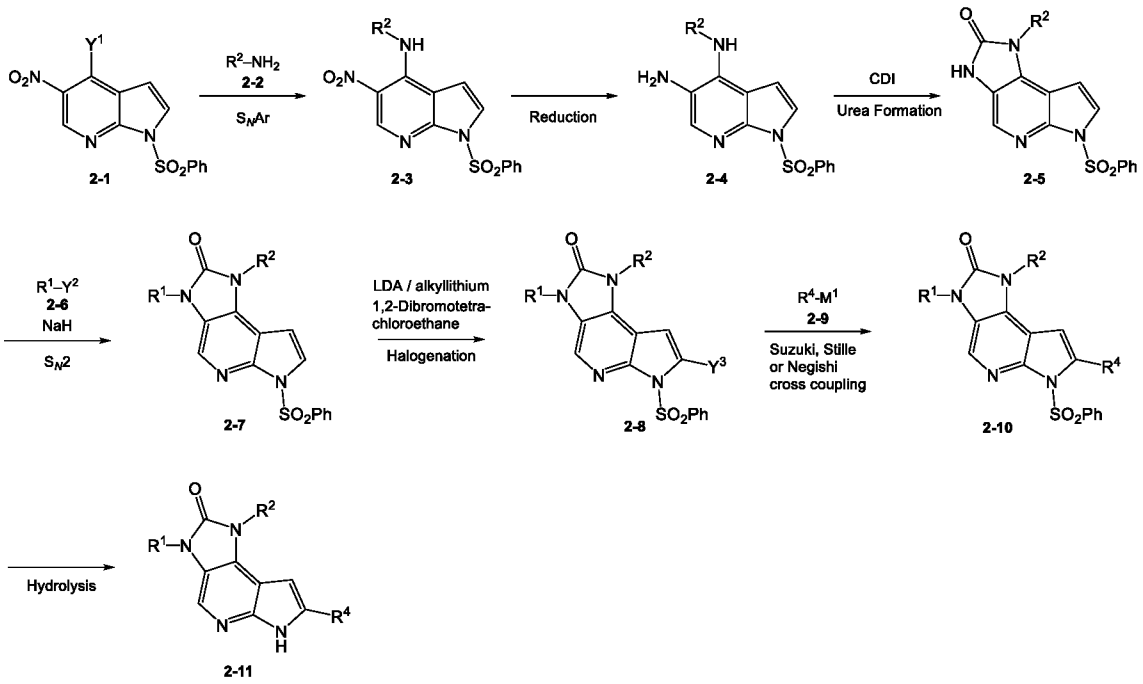
Scheme 1.



Compounds of Formula I can also be prepared, for example, as shown in **Scheme 2** (*e.g.*, compounds of formula **2-11** in **Scheme 2**). Suitable starting materials **2-1**, where Y^1 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs), can be converted to amine **2-3** under standard conditions, such as S_NAr or Buchwald conditions (*e.g.*, in the presence of amine **2-2**). Reduction of nitro **2-3** under standard conditions (*e.g.*, in the presence of Fe, H_2O and NH_4Cl) affords diamine **2-4**. Diamine **2-4** can be converted to cyclic urea **2-5** under standard conditions (*e.g.*, in the presence of CDI). Cyclic urea **2-5** can be further substituted to the tetrasubstituted urea **2-7** under standard conditions, such as S_N2 or Buchwald conditions (*e.g.*, in the presence of NaH and halide **1-6**, where Y^2 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs)). Urea **2-7** can be converted to halide **2-8**, where Y^3 is a halogen (*e.g.*, Cl, Br, or I), under standard conditions (*e.g.*, in the presence of LDA or alkyllithium, 1,2-dibromotetrachloroethane in the case of bromination). Halide **2-8** can be coupled with substituted metal **2-9** (*e.g.*, M^1 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with

dichloromethane and a base (*e.g.*, a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to give compound **2-10**. Deprotection of compound **2-10** under standard hydrolysis conditions (*e.g.*, in the presence of water and sodium hydroxide) affords compound **2-11**.

Scheme 2.

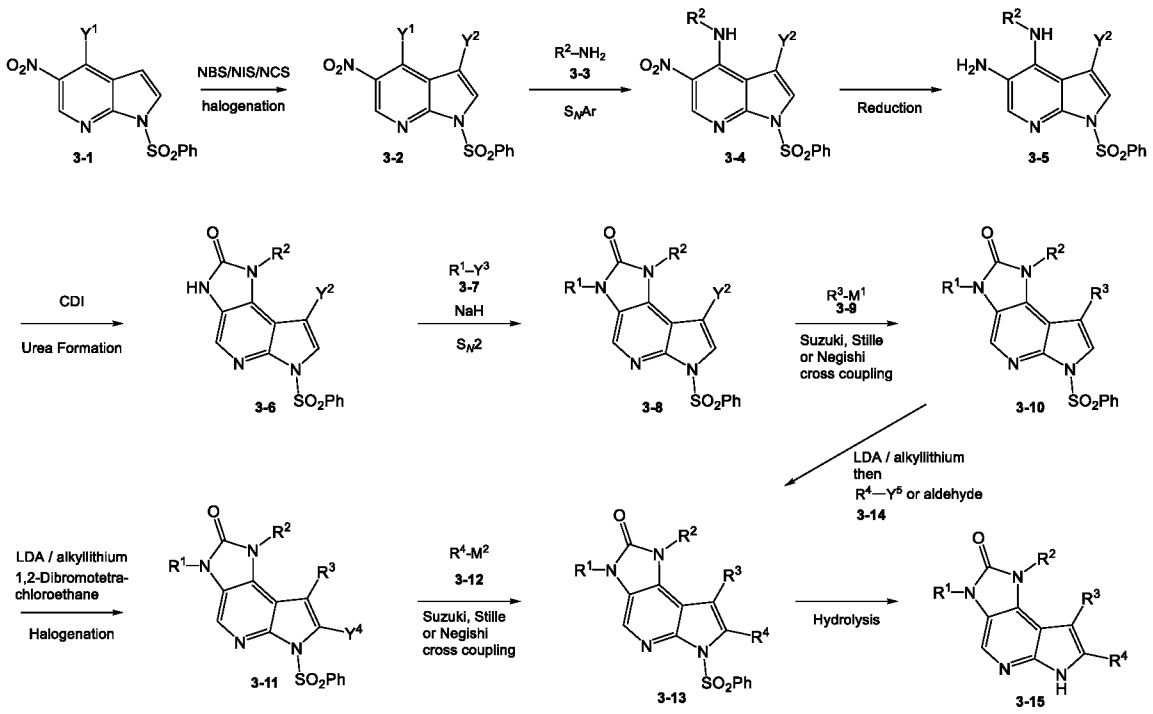


Compounds of Formula I can also be prepared, for example, as shown in **Scheme 3** (*e.g.*, compounds of formula **3-15** in **Scheme 3**). Suitable starting materials **3-1**, where Y^1 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs), can be converted to dihalide **3-2**, where Y^2 is a halogen (*e.g.*, Cl, Br, or I) under standard halogenation conditions (*e.g.*, in the presence of NBS or NIS or NCS). Dihalide **3-2** can be converted to amine **3-4** under standard S_NAr conditions (*e.g.*, in the presence of amine **3-3**). Reduction of compound **3-4** under standard conditions (*e.g.*, in the presence of Fe, H_2O and NH_4Cl) affords diamine **3-5**. Diamine **3-5** can be converted to cyclic urea **3-6** under standard conditions (*e.g.*, in the presence of CDI). Cyclic urea **3-6** can be further substituted to afford the tetrasubstituted urea **3-8** under standard S_N2 conditions (*e.g.*, in the presence of NaH and halide **3-7**, where Y^3 is a

halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs)). Halo-urea **3-8** can be coupled with a substituted metal **3-9** (*e.g.*, M^1 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (*e.g.*, a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (e.g., in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **3-10**. Compound **3-10** can be converted to halide **3-11**, where Y^4 is a halogen (*e.g.*, Cl, Br, or I), under standard conditions (*e.g.*, in the presence of LDA or alkyllithium, 1,2-dibromotetrachloroethane in the case of bromination). Halide **3-11** can be coupled with substituted metal **3-12** (*e.g.*, M^2 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (*e.g.*, a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **3-13**. Alternatively, Compound **3-10** can be converted directly to compoud **3-13** by treating with halide or aldehyde **3-14**, where Y^5 is a halogen (*e.g.*, Cl, Br, I) or pseudohalogen (*e.g.*, OTf or OMs), under standard conditions (*e.g.*, in the presence of LDA or alkyllithium, addition of an alkyl halide in the case of S_N2 reaction, an acyl halide/carbamoyl halide/chloroformate/sulfonyl halide in the case of nucleophilic acyl substitution, an aldehyde in the case of nucleophilic addition). Deprotection of

compound **3-13** under standard hydrolysis conditions (*e.g.*, in the presence of water and sodium hydroxide) affords compound **3-15**.

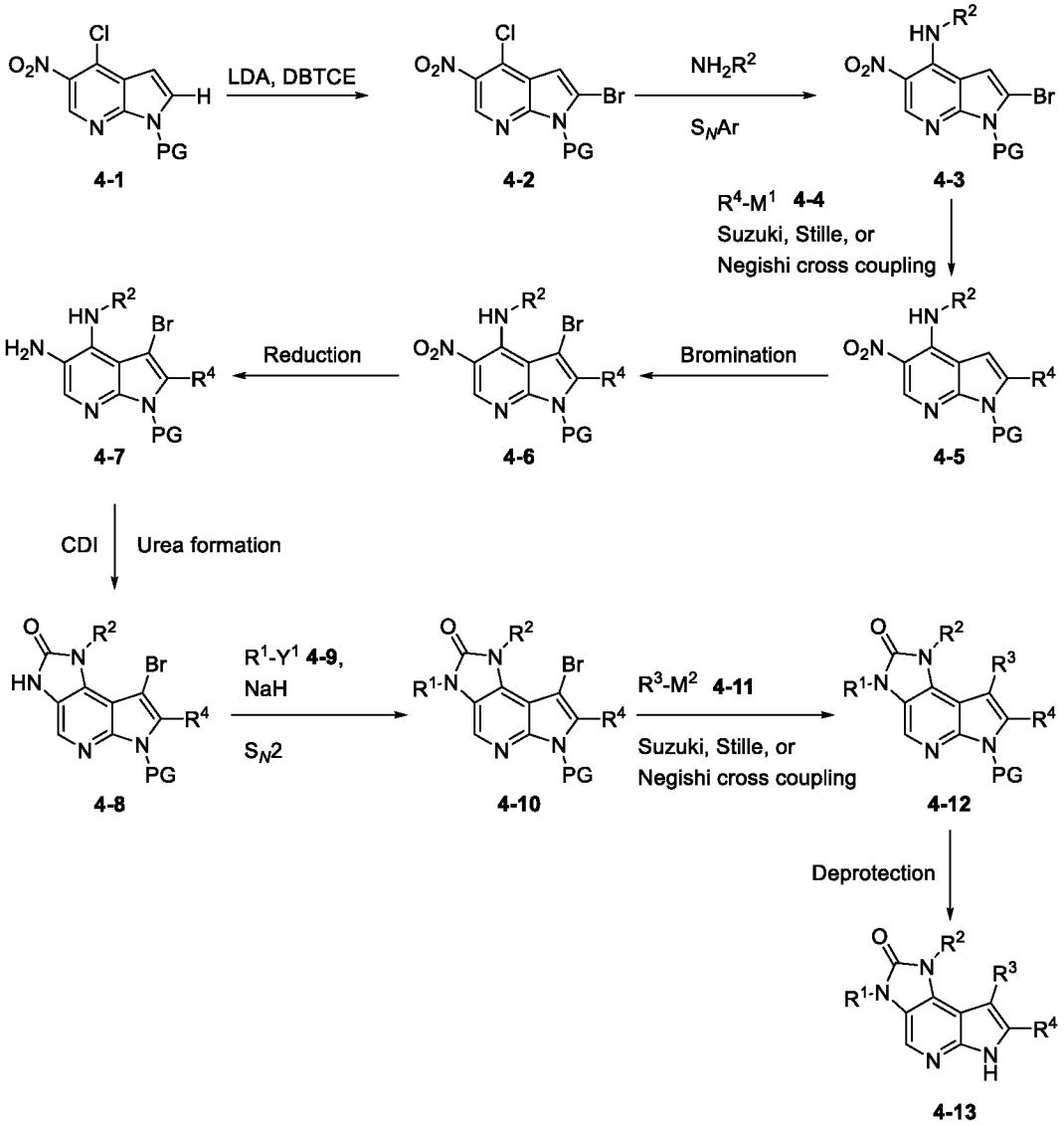
Scheme 3.



Compounds of Formula I can also be prepared, for example, as shown in **Scheme 4** (*e.g.*, compounds of formula **4-13** in **Scheme 4**). The 4-chloro-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine with a suitable protection group such as, but not limited to benzenesulfonyl (compound **4-1**), can be treated with lithium diisopropyl amide solution and a suitable bromination reagent (*e.g.* dibromotetrachloroethane) to generate bromide **4-2**. Compound **4-2** can be converted to amine **4-3** under standard conditions, such as S_NAr or Buchwald conditions (*e.g.*, in the presence of amines of formula NH_2R^2). Compound **4-3** can be coupled with substituted metal **4-4** (*e.g.*, M^1 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (e.g., a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a

palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **4-5**. Compound **4-5** can be brominated with a suitable reagent such as bromine to give **4-6**. Reduction of the nitro group of **4-6** under standard conditions (*e.g.*, in the presence of Fe, H_2O and NH_4Cl or tin chloride) affords diamine **4-7**. Diamine **4-7** can be converted to cyclic urea **4-8** under standard conditions (*e.g.*, in the presence of CDI). Cyclic urea **4-8** can be further substituted to the tetrasubstituted urea **4-10** under standard conditions, such as S_N2 or Buchwald conditions (*e.g.*, in the presence of NaH and halide **4-9**, where Y^1 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs)). Compound **4-10** can be coupled with substituted metal **4-11** (*e.g.*, M^2 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (e.g., a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **4-12**. Finally, compound **4-12** can be deprotected under standard hydrolysis conditions (*e.g.*, in the presence of water and sodium hydroxide when the protecting group is benzenesulfonyl) to give compounds of **4-13**.

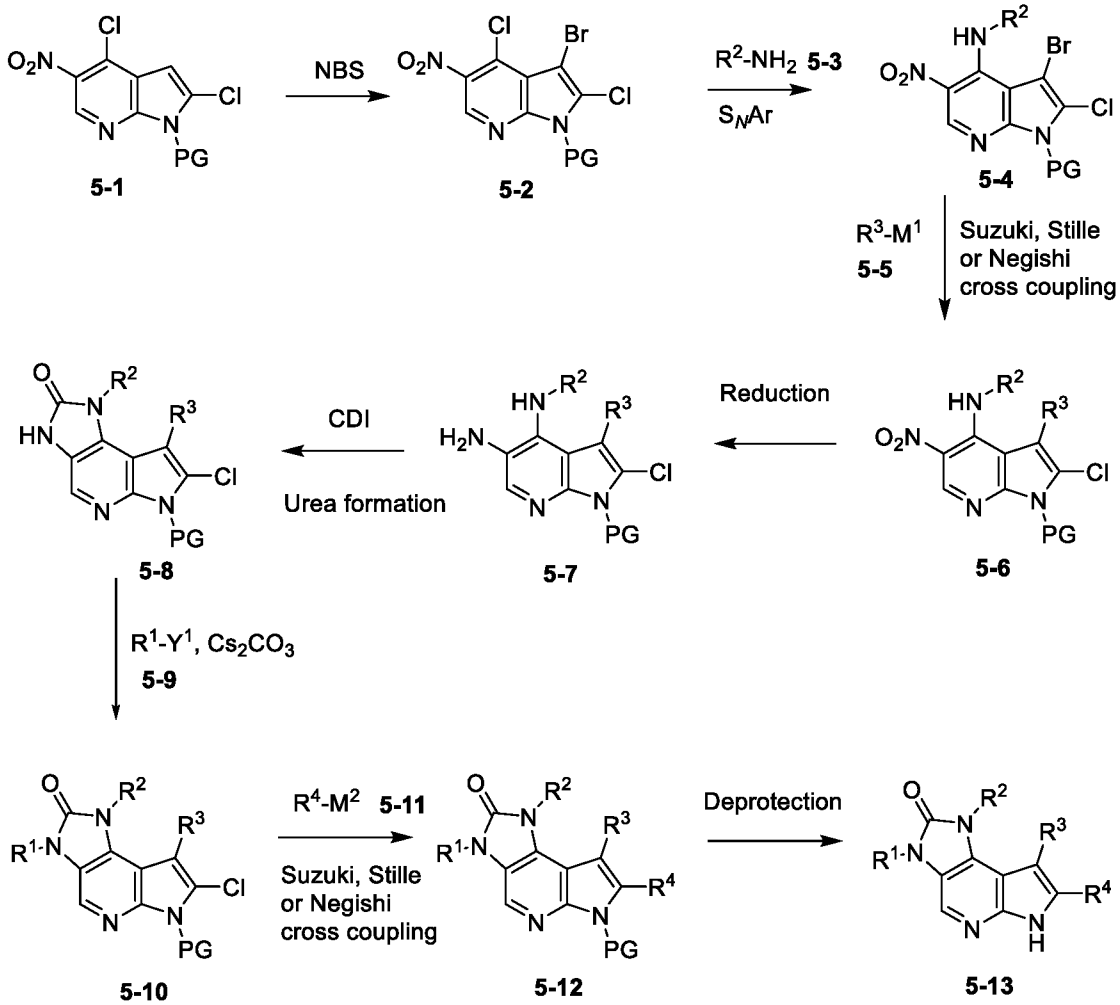
Scheme 4.



Compounds of Formula I can also be prepared, for example, as shown in **Scheme 5** (*e.g.*, compounds of formula **5-13** in **Scheme 5**). The 2,4-dichloro-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine with a suitable protection group such as, but not limited to, trimethylsilylethoxymethyl (SEM) (compound **5-1**), can be converted to dihalide **5-2**, under standard bromination conditions (*e.g.*, in the presence of NBS). Dihalide **5-2** can be converted to amine **5-4** under standard S_NAr conditions (*e.g.*, in the presence of amine **5-3**). Amine **5-4** can be coupled with a substituted metal **5-5** (*e.g.*, M^1 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0),

dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (*e.g.*, a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (e.g., in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **5-6**. Reduction of compound **5-6** under standard conditions (*e.g.*, in the presence of Fe, H_2O and NH_4Cl) affords diamine **5-7**. Diamine **5-7** can be converted to cyclic urea **5-8** under standard conditions (*e.g.*, in the presence of CDI). Cyclic urea **5-8** can be further substituted to afford the tetrasubstituted urea **5-10** under standard S_N2 conditions (*e.g.*, in the presence of $CsCO_3$ and halide **5-9**, where Y^1 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs)). Chloride **5-10** can be coupled with substituted metal **5-11** (*e.g.*, M^2 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (*e.g.*, a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **5-12**. Compound **5-12** can be deprotected under standard conditions (*e.g.*, an initial treatment with trifluoroacetic acid, followed by hydrolysis conditions using water and sodium hydroxide when the protecting group is SEM) to give compounds of **5-13**.

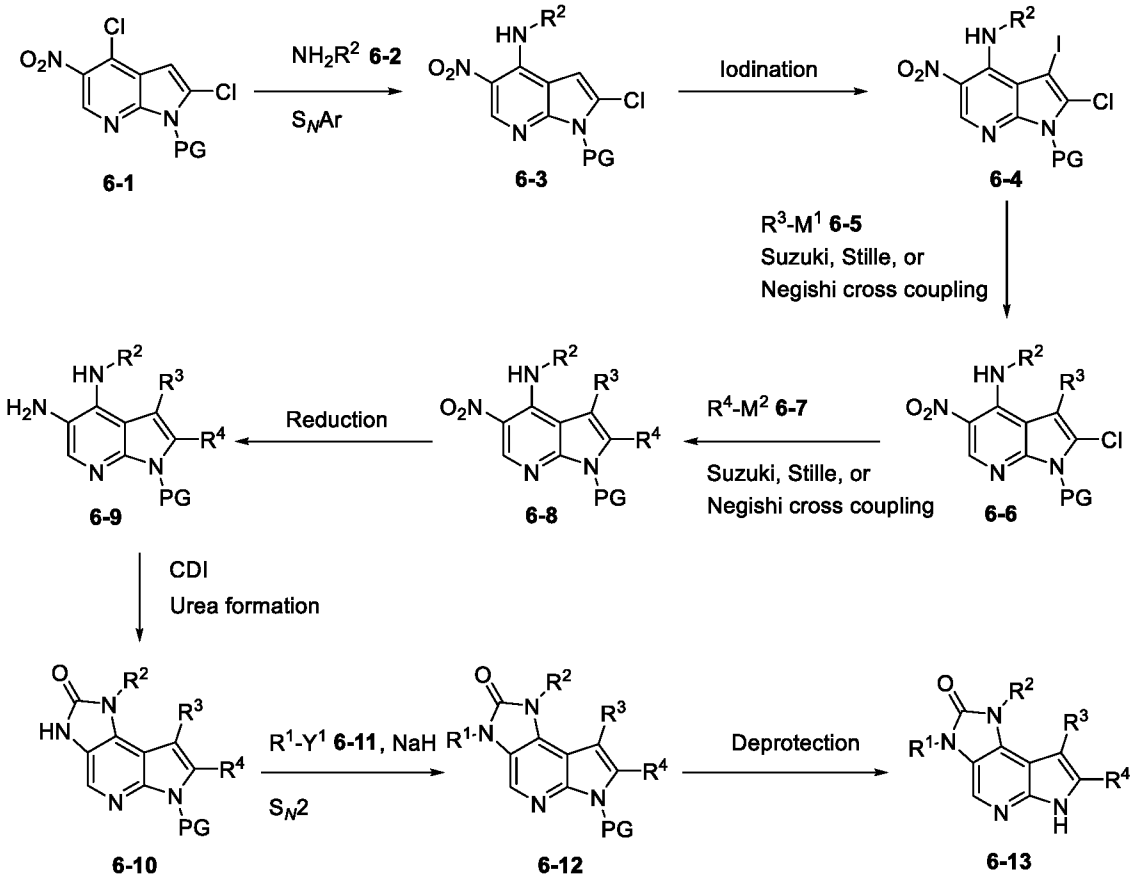
Scheme 5.



Compounds of Formula I can also be prepared, for example, as shown in **Scheme 6** (*e.g.*, compounds of formula **6-13** in **Scheme 6**). Compound **6-1** with a suitable protection group such as, but not limited to 2-(trimethylsilyl)ethoxymethyl (SEM), can be converted to amine **6-3** under standard S_NAr conditions (*e.g.*, in the presence of amine **6-2**). Amine **6-3** can be converted to iodide **6-4** under standard iodination conditions (*e.g.*, in the presence of NIS). Iodide **6-4** can be coupled with substituted metal **6-5** (*e.g.*, M^1 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (e.g., a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a

palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **6-6**. Chloride **6-6** can be coupled with substituted metal **6-7** (*e.g.*, M^2 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (e.g., a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **6-8**. Reduction of compound **6-8** under standard conditions (*e.g.*, using hydrogen gas in the presence of Pd) affords diamine **6-9**. Diamine **6-9** can be converted to cyclic urea **6-10** under standard conditions (*e.g.*, in the presence of CDI). Cyclic urea **6-10** can be further substituted to the tetrasubstituted urea **6-12** under standard conditions (*e.g.*, in the presence of NaH and halide **6-11**, where Y^1 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs)). Compound **6-12** can be deprotected under standard conditions (*e.g.*, for SEM, an initial treatment with trifluoroacetic acid, followed by hydrolysis conditions using water and sodium hydroxide) to give compound **6-13**.

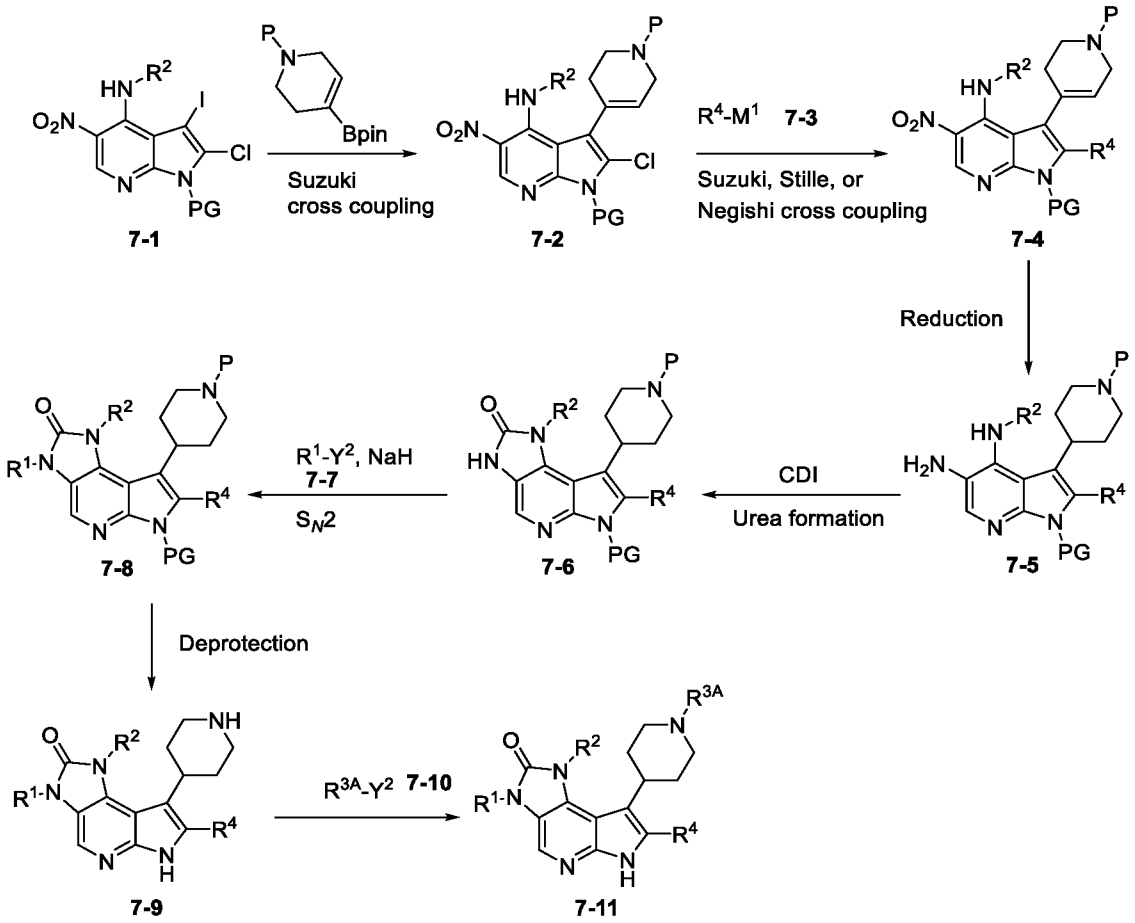
Scheme 6.



Compounds of Formula I can also be prepared, for example, as shown in **Scheme 7** (*e.g.*, compounds of formula **7-11** in **Scheme 7**), when R^2 is a piperidine derivative. Intermediate **7-1** (**6-4** in **Scheme 6**) with a suitable protection group such as, but not limited to 2-(trimethylsilyl)ethoxymethyl, can be converted to compound **7-2** under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane and a base (e.g., a carbonate base, such as sodium carbonate or potassium carbonate)). Compound 7-2 can be coupled with substituted metal **7-3** (*e.g.*, M^1 is $B(OH)_2$, Bpin, BF_3K, $Sn(Bu)_3$, or Zn) under standard Suzuki coupling conditions (*e.g.*, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with

dichloromethane and a base (e.g., a carbonate base, such as sodium carbonate or potassium carbonate)) or standard Stille coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0)) or standard Negishi coupling conditions (*e.g.*, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) to afford compound **7-4**. Reduction of the olefin and nitro group of **7-4** under standard conditions (*e.g.*, using hydrogen gas in the presence of Pd) affords compound **7-5**. Diamine **7-5** can be converted to cyclic urea **7-6** under standard conditions (*e.g.*, in the presence of CDI). Cyclic urea **7-6** can be further substituted to the tetrasubstituted urea **7-8** under standard conditions, such as S_N2 (*e.g.*, in the presence of NaH and halide **7-7**, where Y^2 is a halogen (*e.g.*, Cl, Br, or I) or pseudohalogen (*e.g.*, OTf or OMs)). Compound **7-8** can be deprotected under standard conditions (*e.g.*, for 2-(trimethylsilyl)ethoxymethyl, an initial treatment with trifluoroacetic acid, followed by hydrolysis conditions using water and sodium hydroxide) to give compounds of **7-9**. Finally, compound **7-9** can be reacted with reactive electrophiles **7-10** to give compounds (*e.g.*, amides, sulfonamides, carbamates, etc) **7-11**.

Scheme 7.



The reactions for preparing compounds described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, (e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature). A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

The expressions, "ambient temperature" or "room temperature" or "rt" as used herein, are understood in the art, and refer generally to a temperature, e.g., a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

Preparation of compounds described herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., Wiley & Sons, Inc., New York (1999).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectroscopy (LCMS), or thin layer chromatography (TLC). Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) and normal phase silica chromatography.

Methods of Use

The compounds described herein can inhibit the activity of the V617F variant of the protein-tyrosine kinase JAK2 (*i.e.*, "V617F" or "JAK2V617F"). Compounds which inhibit V617F are useful in providing a means of preventing the growth or inducing apoptosis in tumors, particularly by inhibiting angiogenesis. It is therefore anticipated that the compounds of the disclosure are useful in treating or preventing proliferative disorders such as cancers. In particular tumors with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the inhibitors.

In certain embodiments, the disclosure provides a method for treating a V617F-related disorder in a patient in need thereof, comprising the step of administering to said patient a compound of the disclosure, or a pharmaceutically acceptable composition thereof.

Myeloproliferative diseases (MPD) are multipotent hematopoietic stem cell disorders characterized by excess production of various blood cells. MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic

myelofibrosis (IMF). JAK2 V617F mutation is reported in about 95% of patients with PV, in 35% to 70% of patients with ET, and 50% of patients with IMF. Also, JAK2 exon 12 mutations are detected in some of the V617F-negative PV patients (Ma et al., J. Mol. Diagn., 11: 49-53, 2009). In some embodiments, the compounds of the disclosure can be useful in the treatment of myeloproliferative disorders (*e.g.*, myeloproliferative neoplasms) in a patient in need thereof, such as polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia (MMM), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), and the like.

In some embodiments, the myeloproliferative disorder is a myeloproliferative neoplasm.

In some embodiments, the myeloproliferative disorder is myelofibrosis (*e.g.*, primary myelofibrosis (PMF) or post polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET MF)).

In some embodiments, the myeloproliferative disorder is primary myelofibrosis (PMF).

In some embodiments, the myeloproliferative disorder is post- essential thrombocythemia myelofibrosis (Post-ET MF).

In some embodiments, the myeloproliferative disorder is post polycythemia vera myelofibrosis (Post-PV MF).

In some embodiments, the myeloproliferative disorder is selected from primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET).

In some embodiments, the myeloproliferative neoplasm is primary myelofibrosis (PMF).

In some embodiments, the myeloproliferative neoplasm is polycythemia vera (PV).

In some embodiments, the myeloproliferative neoplasm is essential thrombocythemia (ET).

Myeloproliferative diseases include disorders of a bone marrow or lymph node-derived cell type, such as a white blood cell. A myeloproliferative disease can

manifest by abnormal cell division resulting in an abnormal level of a particular hematological cell population. The abnormal cell division underlying a proliferative hematological disorder is typically inherent in the cells and not a normal physiological response to infection or inflammation. Leukemia is a type of myeloproliferative disease. Exemplary myeloproliferative diseases include, but are not limited to, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), hairy cell leukemia, leukemic manifestations of lymphomas, multiple myeloma, polycythemia vera (PV), essential thrombocythemia (ET), idiopathic myelofibrosis (IMF), hypereosinophilic syndrome (HES), chronic neutrophilic leukemia (CNL), myelofibrosis with myeloid metaplasia (MMM), chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia, chronic basophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis (SM), and unclassified myeloproliferative diseases (UMPD or MPD-NC). Lymphoma is a type of proliferative disease that mainly involves lymphoid organs, such as lymph nodes, liver, and spleen. Exemplary proliferative lymphoid disorders include lymphocytic lymphoma (also called chronic lymphocytic leukemia), follicular lymphoma, large cell lymphoma, Burkitt's lymphoma, marginal zone lymphoma, lymphoblastic lymphoma (also called acute lymphoblastic lymphoma).

For example, the compounds of the disclosure are useful in the treatment of cancer. Example cancers include bladder cancer (e.g., urothelial carcinoma, squamous cell carcinoma, adenocarcinoma), breast cancer (e.g., hormone R positive, triple negative), cervical cancer, colorectal cancer, cancer of the small intestine, colon cancer, rectal cancer, cancer of the anus, endometrial cancer, gastric cancer (e.g., gastrointestinal stromal tumors), head and neck cancer (e.g., cancers of the larynx, hypopharynx, nasopharynx, oropharynx, lips, and mouth, squamous head and neck cancers), kidney cancer (e.g., renal cell carcinoma, urothelial carcinoma, sarcoma, Wilms tumor), liver cancer (e.g., hepatocellular carcinoma, cholangiocellular carcinoma (e.g., intrahepatic, hilar or perihilar, distal extrahepatic), liver angiosarcoma, hepatoblastoma), lung cancer (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, pleuropulmonary blastoma),

ovarian cancer, prostate cancer, testicular cancer, uterine cancer, vulvar cancer, esophageal cancer, gall bladder cancer, pancreatic cancer (e.g. exocrine pancreatic carcinoma), stomach cancer, thyroid cancer, parathyroid cancer, neuroendocrine cancer (e.g., pheochromocytoma, Merkel cell cancer, neuroendocrine carcinoma), skin cancer (e.g., squamous cell carcinoma, Kaposi sarcoma, Merkel cell skin cancer), and brain cancer (e.g., astrocytoma, medulloblastoma, ependymoma, neuro-ectodermal tumors, pineal tumors).

Further example cancers include hematopoietic malignancies such as leukemia or lymphoma, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, acute myeloid leukemia (AML), B-cell lymphoma, cutaneous T-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-Hodgkin's lymphoma, myeloproliferative neoplasms (*e.g.*, 8p11 myeloproliferative syndrome, polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)), myelodysplastic syndrome, chronic eosinophilic leukemia, Waldenstrom's Macroglubulinemia, hairy cell lymphoma, chronic myelogenic lymphoma, acute lymphoblastic lymphoma, AIDS-related lymphomas, and Burkitt's lymphoma.

In certain embodiments, provided herein is a method of treating cancer comprising administering to a patient in need thereof a therapeutically effect amount of a compound of the disclosure. In certain embodiments, the cancer is selected from T lymphoblastic lymphoma, glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, and osteosarcoma.

Other cancers treatable with the compounds of the disclosure include tumors of the eye, glioblastoma, melanoma, leiomyosarcoma, and urothelial carcinoma (e.g., ureter, urethra, bladder, urachus).

The compounds of the disclosure can also be useful in the inhibition of tumor metastases.

In some embodiments, the compounds of the disclosure as described herein can be used to treat Alzheimer's disease, HIV, or tuberculosis.

In some embodiments, the compounds of the disclosure can be useful in the treatment of myelodysplastic syndrome (MDS) in a patient in need thereof. In some embodiments, said patient having the myelodysplastic syndrome (MDS) is red blood cell transfusion dependent.

As used herein, myelodysplastic syndromes are intended to encompass heterogeneous and clonal hematopoietic disorders that are characterized by ineffective hematopoiesis on one or more of the major myeloid cell lineages. Myelodysplastic syndromes are associated with bone marrow failure, peripheral blood cytopenias, and a propensity to progress to acute myeloid leukemia (AML). Moreover, clonal cytogenetic abnormalities can be detected in about 50% of cases with MDS. In 1997, The World Health Organization (WHO) in conjunction with the Society for Hematopathology (SH) and the European Association of Hematopathology (EAHP) proposed new classifications for hematopoietic neoplasms (Harris, et al., *J Clin Oncol* 1999;17:3835-3849; Vardiman, et al., *Blood* 2002;100:2292-2302). For MDS, the WHO utilized not only the morphologic criteria from the French-American-British (FAB) classification but also incorporated available genetic, biologic, and clinical characteristics to define subsets of MDS (Bennett, et al., *Br. J. Haematol.* 1982;51:189-199). In 2008, the WHO classification of MDS (Table 1) was further refined to allow precise and prognostically relevant subclassification of unilineage dysplasia by incorporating new clinical and scientific information (Vardiman, et al., *Blood* 2009;114:937-951; Swerdlow, et al., WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th Edition. Lyon France: IARC Press; 2008:88-103; Bunning and Germing, "Myelodysplastic syndromes/neoplasms" in Chapter 5, Swerdlow, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. (ed. 4th edition): Lyon, France: IARC Press;2008:88-103).

Table 1. 2008 WHO Classification for De Novo Myelodysplastic Syndrome

Subtype	Blood	Bone Marrow
Refractory cytopenia with unilineage dysplasia (RCUD)	Single or Bicytopenia	Dysplasia in ≥ 10% of 1 cell line, < 5% blasts
Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	≥ 15% of erythroid precursors w/ring sideroblasts, erythroid dysplasia only, < 5% blasts
Refractory cytopenia with multilineage dysplasia	Cytopenia(s), < 1 × 10^9/L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 hematopoietic lineages, ± 15% ring sideroblasts, < 5% blasts

Subtype	Blood	Bone Marrow
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s), ≤ 2% to 4% blasts, < 1×10^9/L monocytes	Unilineage or multilineage dysplasia, No Auer rods, 5% to 9% blasts
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s), ≤ 5% to 19% blasts, < 1×10^9/L monocytes	Unilineage or multilineage dysplasia, ± Auer rods, 10% to 19% blasts
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias	Unilineage or no dysplasia but characteristic MDS cytogenetics, < 5% blasts
MDS associated with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid. Isolated del(5q), < 5% blasts

In some embodiments, the myelodysplastic syndrome is refractory cytopenia with unilineage dysplasia (RCUD).

In some embodiments, the myelodysplastic syndrome is refractory anemia with ring sideroblasts (RARS).

In some embodiments, the myelodysplastic syndrome is refractory anemia with ring sideroblasts associated with thrombocytosis (RARS-T).

In some embodiments, the myelodysplastic syndrome is refractory cytopenia with multilineage dysplasia.

In some embodiments, the myelodysplastic syndrome is refractory anemia with excess blasts-1 (RAEB-1).

In some embodiments, the myelodysplastic syndrome is refractory anemia with excess blasts-2 (RAEB-2).

In some embodiments, the myelodysplastic syndrome is myelodysplastic syndrome, unclassified (MDS-U).

In some embodiments, the myelodysplastic syndrome is myelodysplastic syndrome associated with isolated del(5q).

In some embodiments, the myelodysplastic syndrome is refractory to erythropoiesis-stimulating agents.

In some embodiments, the compounds of the disclosure can be useful in the treatment of myeloproliferative disorder/myelodysplastic overlap syndrome (MPD/MDS overlap syndrome).

In some embodiments, the compounds of the disclosure can be useful in the treatment of leukemia.

In some embodiments, the compounds of the disclosure can be useful in the treatment of acute myeloid leukemia (AML).

In addition to oncogenic neoplasms, the compounds of the disclosure can be useful in the treatment of skeletal and chondrocyte disorders including, but not limited to, achrondroplasia, hypochondroplasia, dwarfism, thanatophoric dysplasia (TD) (clinical forms TD I and TD II), Apert syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, Pfeiffer syndrome, and craniosynostosis syndromes.

The compounds provided herein may further be useful in the treatment of fibrotic diseases, such as where a disease symptom or disorder is characterized by fibrosis. Example fibrotic diseases include liver cirrhosis, glomerulonephritis, pulmonary fibrosis, systemic fibrosis, rheumatoid arthritis, and wound healing.

In some embodiments, the compounds provided herein can be used in the treatment of a hypophosphatemia disorder such as, for example, X-linked hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, and autosomal dominant hypophosphatemic rickets, or tumor-induced osteromalacia.

In some embodiments, provided herein is a method of increasing survival or progression-free survival in a patient, comprising administering a compound provided herein to the patient. In some embodiments, the patient has cancer. In some embodiments, the patient has a disease or disorder described herein. As used herein, progression-free survival refers to the length of time during and after the treatment of a solid tumor that a patient lives with the disease but it does not get worse. Progression-free survival can refer to the length of time from first administering the compound until the earlier of death or progression of the disease. Progression of the disease can be defined by RECIST v. 1.1 (Response Evaluation Criteria in Solid Tumors), as assessed by an independent centralized radiological review committee. In some embodiments, administering of the compound results in a progression free survival that is greater than about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 9 months, about 12 months, about 16 months, or about 24 months. In some embodiments, the

administering of the compound results in a progression free survival that is at least about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 9 months, or about 12 months; and less than about 24 months, about 16 months, about 12 months, about 9 months, about 8 months, about 6 months, about 5 months, about 4 months, about 3 months, or about 2 months. In some embodiments, the administering of the compound results in an increase of progression free survival that is at least about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 9 months, or about 12 months; and less than about 24 months, about 16 months, about 12 months, about 9 months, about 8 months, about 6 months, about 5 months, about 4 months, about 3 months, or about 2 months.

The present disclosure further provides a compound described herein, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

The present disclosure further provides use of a compound described herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in any of the methods described herein.

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a V617F variant with a compound described herein includes the administration of a compound described herein to an individual or patient, such as a human, having a V617F variant, as well as, for example, introducing a compound described herein into a sample containing a cellular or purified preparation containing the V617F variant.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent such as an amount of any of the solid forms or salts thereof as disclosed herein that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. An appropriate "effective" amount in any individual case may be determined using techniques known to a person skilled in the art.

The phrase "pharmaceutically acceptable" is used herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the phrase "pharmaceutically acceptable carrier or excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients or carriers are generally safe, non-toxic and neither biologically nor otherwise undesirable and include excipients or carriers that are acceptable for veterinary use as well as human pharmaceutical use. In one embodiment, each component is "pharmaceutically acceptable" as defined herein. See, e.g., *Remington: The Science and Practice of Pharmacy,* 21st *ed.;* Lippincott Williams & Wilkins: Philadelphia, Pa., 2005; *Handbook of Pharmaceutical Excipients, 6th ed.;* Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.;* Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.;* Gibson Ed.; CRC Press LLC: Boca Raton, Fla., 2009.

As used herein, the term "treating" or "treatment" refers to inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology) or ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology

or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

In some embodiments, the compounds of the invention are useful in preventing or reducing the risk of developing any of the diseases referred to herein; *e.g.*, preventing or reducing the risk of developing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the disclosure which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

Combination Therapies

One or more additional pharmaceutical agents or treatment methods such as, for example, anti-viral agents, chemotherapeutics or other anti-cancer agents, immune enhancers, immunosuppressants, radiation, anti-tumor and anti-viral vaccines, cytokine therapy (*e.g.*, IL2, GM-CSF, *etc.*), and/or tyrosine kinase inhibitors can be used in combination with compounds described herein for treatment or prevention of V617F-associated diseases, disorders or conditions, or diseases or conditions as described herein. The agents can be combined with the present compounds in a single dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

Compounds described herein can be used in combination with one or more other kinase inhibitors for the treatment of diseases, such as cancer, that are impacted by multiple signaling pathways. For example, a combination can include one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, TGF-βR, Pim, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IGF-1R, IR-R, PDGFαR, PDGFβR, CSFIR, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, Ron, Sea, TRKA, TRKB, TRKC, FLT3, VEGFR/Flt2, Flt4, EphA1,

EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. Additionally, the solid forms of the inhibitor as described herein can be combined with inhibitors of kinases associated with the PIK3/Akt/mTOR signaling pathway, such as PI3K, Akt (including Akt1, Akt2 and Akt3) and mTOR kinases.

In some embodiments, compounds described herein can be used in combination with one or more inhibitors of the enzyme or protein receptors such as HPK1, SBLB, TUT4, A2A/A2B, CD19, CD47, CDK2, STING, ALK2, LIN28, ADAR1, MAT2a, RIOK1, HDAC8, WDR5, SMARCA2, and DCLK1 for the treatment of diseases and disorders. Exemplary diseases and disorders include cancer, infection, inflammation and neurodegenerative disorders.

In some embodiments, compounds described herein can be used in combination with a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include bromodomain inhibitors, the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, *e.g.*, vorinostat.

For treating cancer and other proliferative diseases, compounds described herein can be used in combination with targeted therapies, including JAK kinase inhibitors (ruxolitinib, additional JAK1/2 and JAK1-selective, baricitinib or itacitinib), Pim kinase inhibitors (e.g., LGH447, INCB053914 and SGI-1776), PI3 kinase inhibitors including PI3K-delta selective and broad spectrum PI3K inhibitors (e.g., INCB50465 and INCB50797), PI3K-gamma inhibitors such as PI3K-gamma selective inhibitors, MEK inhibitors, CSF1R inhibitors (e.g., PLX3397 and LY3022855), TAM receptor tyrosine kinases inhibitors (Tyro-3, Axl, and Mer; e.g., INCB81776), angiogenesis inhibitors, interleukin receptor inhibitors, Cyclin Dependent kinase inhibitors, BRAF inhibitors, mTOR inhibitors, proteasome inhibitors (Bortezomib, Carfilzomib), HDAC-inhibitors (panobinostat, vorinostat), DNA methyl transferase inhibitors, dexamethasone, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors, such as OTX015, CPI-0610, INCB54329 or INCB57643), LSD1 inhibitors (e.g., GSK2979552, INCB59872 and INCB60003), arginase inhibitors (e.g., INCB1158),

indoleamine 2,3-dioxygenase inhibitors (e.g., epacadostat, NLG919 or BMS-986205), PARP inhibiors (e.g., olaparib or rucaparib), and inhibitors of BTK such as ibrutinib.

For treating cancer and other proliferative diseases, compounds described herein can be used in combination with chemotherapeutic agents, agonists or antagonists of nuclear receptors, or other anti-proliferative agents. Compounds described herein can also be used in combination with a medical therapy such as surgery or radiotherapy, *e.g.*, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes.

Examples of suitable chemotherapeutic agents include any of: abarelix, abiraterone, afatinib, aflibercept, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amidox, amsacrine, anastrozole, aphidicolon, arsenic trioxide, asparaginase, axitinib, azacitidine, bevacizumab, bexarotene, baricitinib, bendamustine, bicalutamide, bleomycin, bortezombi, bortezomib, brivanib, buparlisib, busulfan intravenous, busulfan oral, calusterone, camptosar, capecitabine, carboplatin, carmustine, cediranib, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, crizotinib, cyclophosphamide, cytarabine, dacarbazine, dacomitinib, dactinomycin, dalteparin sodium, dasatinib, dactinomycin, daunorubicin, decitabine, degarelix, denileukin, denileukin diftitox, deoxycoformycin, dexrazoxane, didox, docetaxel, doxorubicin, droloxafine, dromostanolone propionate, eculizumab, enzalutamide, epidophyllotoxin, epirubicin, epothilones, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, flutamide, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, idelalisib, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lonafarnib, lomustine, meclorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mithramycin, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, navelbene, necitumumab, nelarabine, neratinib, nilotinib, nilutamide, niraparib, nofetumomab, oserelin, oxaliplatin, paclitaxel, pamidronate, panitumumab, panobinostat, pazopanib, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pilaralisib, pipobroman, plicamycin, ponatinib, porfimer, prednisone, procarbazine, quinacrine, ranibizumab, rasburicase,

regorafenib, reloxafine, revlimid, rituximab, rucaparib, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, tegafur, temozolomide, teniposide, testolactone, tezacitabine, thalidomide, thioguanine, thiotepa, tipifarnib, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, triapine, trimidox, triptorelin, uracil mustard, valrubicin, vandetanib, vinblastine, vincristine, vindesine, vinorelbine, vorinostat, veliparib, talazoparib, and zoledronate.

In some embodiments, compounds described herein can be used in combination with immune checkpoint inhibitors. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3 (e.g., INCAGN2385), TIM3 (e.g., INCB2390), VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40 (e.g., INCAGN1949), GITR (e.g., INCAGN1876) and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the inhibitor of an immune checkpoint molecule is a small molecule PD-L1 inhibitor. In some embodiments, the small molecule PD-L1 inhibitor has an IC50 less than 1 μM, less than 100 nM, less than 10 nM or less than 1 nM in a PD-L1 assay described in US Patent Publication Nos. US 20170107216, US 20170145025, US 20170174671, US 20170174679, US 20170320875, US 20170342060, US 20170362253, and US 20180016260, each of which is incorporated by reference in its entirety for all purposes.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is retifanlimab (also known as MGA012), nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001,

ipilumimab or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD1 antibody is pembrolizumab. In some embodiments, the anti-PD1 antibody is nivolumab. In some embodiments, the anti-PD-1 monoclonal antibody is retifanlimab. In some embodiments, the anti-PD1 antibody is SHR-1210. Other anti-cancer agent(s) include antibody therapeutics such as 4-1BB (e.g. urelumab, utomilumab.

In some embodiments, the compounds of the disclosure can be used in combination with INCB086550.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A or MEDI4736.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab, tremelimumab, AGEN1884, or CP-675,206.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016, LAG525, or INCAGN2385.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIM3, e.g., an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is INCAGN2390, MBG453, or TSR-022.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX518, MK-4166, INCAGN1876, MK-1248, AMG228, BMS-986156, GWN323, or MEDI1873.

In some embodiments, the inhibitor of an immune checkpoint molecule is an agonist of OX40, e.g., OX40 agonist antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562, MOXR-0916, PF-04518600, GSK3174998, or BMS-986178. In some embodiments, the OX40L fusion protein is MEDI6383.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD20, e.g., an anti-CD20 antibody. In some embodiments, the anti-CD20 antibody is obinutuzumab or rituximab.

The compounds of the present disclosure can be used in combination with bispecific antibodies. In some embodiments, one of the domains of the bispecific antibody targets PD-1, PD-L1, CTLA-4, GITR, OX40, TIM3, LAG3, CD137, ICOS, CD3 or TGFβ receptor.

In some embodiments, the compounds of the disclosure can be used in combination with one or more metabolic enzyme inhibitors. In some embodiments, the metabolic enzyme inhibitor is an inhibitor of IDO1, TDO, or arginase. Examples of IDO1 inhibitors include epacadostat, NLG919, BMS-986205, PF-06840003, IOM2983, RG-70099 and LY338196.

In some embodiments, the compounds described herein can be used in combination with one or more agents for the treatment of diseases such as cancer. In some embodiments, the agent is an alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include cyclophosphamide (CY), melphalan (MEL), and bendamustine. In some embodiments, the proteasome inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM).

Suitable antiviral agents contemplated for use in combination with compounds of the present disclosure can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and other antiviral drugs.

Example suitable NRTIs include zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil [bis(POM)-PMEA]; lobucavir (BMS-180194); BCH-10652; emitricitabine [(-)-FTC]; beta-L-FD4 (also called beta-L-D4C and named beta-L-2', 3'-dicleoxy-5-fluoro-cytidene); DAPD, ((-)-beta-D-2,6,-diamino-purine dioxolane); and lodenosine (FddA). Typical suitable NNRTIs include nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione);

and (+)-calanolide A (NSC-675451) and B. Typical suitable protease inhibitors include saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfnavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; and AG-1 549. Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No.11607.

Suitable agents for use in combination with compounds described herein for the treatment of cancer include chemotherapeutic agents, targeted cancer therapies, immunotherapies or radiation therapy. Compounds described herein may be effective in combination with anti-hormonal agents for treatment of breast cancer and other tumors. Suitable examples are anti-estrogen agents including but not limited to tamoxifen and toremifene, aromatase inhibitors including but not limited to letrozole, anastrozole, and exemestane, adrenocorticosteroids (e.g. prednisone), progestins (e.g. megastrol acetate), and estrogen receptor antagonists (e.g. fulvestrant). Suitable anti-hormone agents used for treatment of prostate and other cancers may also be combined with compounds described herein. These include anti-androgens including but not limited to flutamide, bicalutamide, and nilutamide, luteinizing hormone-releasing hormone (LHRH) analogs including leuprolide, goserelin, triptorelin, and histrelin, LHRH antagonists (e.g. degarelix), androgen receptor blockers (e.g. enzalutamide) and agents that inhibit androgen production (e.g. abiraterone).

The compounds described herein may be combined with or in sequence with other agents against membrane receptor kinases especially for patients who have developed primary or acquired resistance to the targeted therapy. These therapeutic agents include inhibitors or antibodies against EGFR, Her2, VEGFR, c-Met, Ret, IGFR1, or Flt-3 and against cancer-associated fusion protein kinases such as Bcr-Abl and EML4-Alk. Inhibitors against EGFR include gefitinib and erlotinib, and inhibitors against EGFR/Her2 include but are not limited to dacomitinib, afatinib, lapitinib and neratinib. Antibodies against the EGFR include but are not limited to cetuximab, panitumumab and necitumumab. Inhibitors of c-Met may be used in combination with FGFR inhibitors. These include onartumzumab, tivantnib, and INC-280. Agents against Abl (or Bcr-Abl) include imatinib, dasatinib, nilotinib, and ponatinib and those against Alk (or EML4-ALK) include crizotinib.

Angiogenesis inhibitors may be efficacious in some tumors in combination with inhibitors described herein. These include antibodies against VEGF or VEGFR or kinase inhibitors of VEGFR. Antibodies or other therapeutic proteins against VEGF include bevacizumab and aflibercept. Inhibitors of VEGFR kinases and other anti-angiogenesis inhibitors include but are not limited to sunitinib, sorafenib, axitinib, cediranib, pazopanib, regorafenib, brivanib, and vandetanib

Activation of intracellular signaling pathways is frequent in cancer, and agents targeting components of these pathways have been combined with receptor targeting agents to enhance efficacy and reduce resistance. Examples of agents that may be combined with compounds described herein include inhibitors of the PI3K-AKT-mTOR pathway, inhibitors of the Raf-MAPK pathway, inhibitors of JAK-STAT pathway, and inhibitors of protein chaperones and cell cycle progression.

Agents against the PI3 kinase include but are not limited topilaralisib, idelalisib, buparlisib. Inhibitors of mTOR such as rapamycin, sirolimus, temsirolimus, and everolimus may be combined with compounds described herein. Other suitable examples include but are not limited to vemurafenib and dabrafenib (Raf inhibitors) and trametinib, selumetinib and GDC-0973 (MEK inhibitors). Inhibitors of one or more JAKs (e.g., ruxolitinib, baricitinib, tofacitinib), Hsp90 (e.g., tanespimycin), cyclin dependent kinases (e.g., palbociclib), HDACs (e.g., panobinostat), PARP (e.g., olaparib), and proteasomes (e.g., bortezomib, carfilzomib) can also be combined with compounds described herein. In some embodiments, the JAK inhibitor is selective for JAK1 over JAK2 and JAK3.

Other suitable agents for use in combination with compounds described herein include chemotherapy combinations such as platinum-based doublets used in lung cancer and other solid tumors (cisplatin or carboplatin plus gemcitabine; cisplatin or carboplatin plus docetaxel; cisplatin or carboplatin plus paclitaxel; cisplatin or carboplatin plus pemetrexed) or gemcitabine plus paclitaxel bound particles.

Suitable chemotherapeutic or other anti-cancer agents include, for example, alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes) such as uracil mustard, chlormethine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, pipobroman,

triethylene-melamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, and temozolomide.

Other suitable agents for use in combination with compounds described herein include steroids including 17 alpha-ethinylestradiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, and medroxyprogesteroneacetate.

Other suitable agents for use in combination with compounds described herein include: dacarbazine (DTIC), optionally, along with other chemotherapy drugs such as carmustine (BCNU) and cisplatin; the "Dartmouth regimen," which consists of DTIC, BCNU, cisplatin and tamoxifen; a combination of cisplatin, vinblastine, and DTIC; or temozolomide. Compounds described herein may also be combined with immunotherapy drugs, including cytokines such as interferon alpha, interleukin 2, and tumor necrosis factor (TNF) in.

Suitable chemotherapeutic or other anti-cancer agents include, for example, antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) such as methotrexate, 5-fluorouracil, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, and gemcitabine.

Suitable chemotherapeutic or other anti-cancer agents further include, for example, certain natural products and their derivatives (e.g., vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins) such as vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel, mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, interferons (especially IFN-a), etoposide, and teniposide.

Other cytotoxic agents include navelbene, CPT-11, anastrazole, letrazole, capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine.

Also suitable are cytotoxic agents such as epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response

modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4, 4-1BB, PD-L1 and PD-1 antibodies, or antibodies to cytokines (IL-10, TGF-β, etc.).

Other anti-cancer agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4.

Other anti-cancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer.

Anti-cancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MARTI and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

The compounds of the present disclosure can be used in combination with bone marrow transplant for the treatment of a variety of tumors of hematopoietic origin (see *e.g.*, U.S. Patent Nos.: 9,233,985, 10,065,974, 10,287,303, 8,524,867, the disclosures of which are incorporated by reference herein in their entireties).

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR, e.g., 1996 edition, Medical Economics Company, Montvale, NJ), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

As provided throughout, the additional compounds, inhibitors, agents, etc. can be combined with the present compound in a single or continuous dosage form, or they can be administered simultaneously or sequentially as separate dosage forms.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the disclosure can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral, or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This disclosure also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the disclosure or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions of the disclosure, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

The compounds of the disclosure may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the disclosure can be prepared by processes known in the art, e.g., see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the disclosure can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compositions of the disclosure contain from about 5 to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 5 to about 10, about 10 to about 15, about 15 to about 20, about 20 to about 25, about 25 to about 30, about

30 to about 35, about 35 to about 40, about 40 to about 45, or about 45 to about 50 mg of the active ingredient.

In some embodiments, the compositions of the disclosure contain from about 50 to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 50 to about 100, about 100 to about 150, about 150 to about 200, about 200 to about 250, about 250 to about 300, about 350 to about 400, or about 450 to about 500 mg of the active ingredient.

In some embodiments, the compositions of the disclosure contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 500 to about 550, about 550 to about 600, about 600 to about 650, about 650 to about 700, about 700 to about 750, about 750 to about 800, about 800 to about 850, about 850 to about 900, about 900 to about 950, or about 950 to about 1000 mg of the active ingredient.

Similar dosages may be used of the compounds described herein in the methods and uses of the disclosure.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present disclosure. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present disclosure.

The tablets or pills of the present disclosure can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present disclosure can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g. glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose, and the like. In

some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the compound of the disclosure. The topical formulations can be suitably packaged in tubes of, for example, 100 g which are optionally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present disclosure can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the disclosure in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the disclosure can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some

typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compositions of the disclosure can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed herein.

Labeled Compounds and Assay Methods

Another aspect of the present disclosure relates to labeled compounds of the disclosure (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating V617F in tissue samples, including human, and for identifying V617F inhibitors by binding of a labeled compound. Substitution of one or more of the atoms of the compounds of the present disclosure can also be useful in generating differentiated ADME (Adsorption, Distribution, Metabolism and Excretion.) Accordingly, the present disclosure includes V617F assays that contain such labeled or substituted compounds.

The present disclosure further includes isotopically-labeled compounds of the disclosure. An "isotopically" or "radio-labeled" compound is a compound of the disclosure where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present disclosure include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced by deuterium atoms (e.g., one or more hydrogen atoms of a C_{1-6} alkyl group

of Formula I can be optionally substituted with deuterium atoms, such as $-CD_3$ (*i.e.*, trideuteromethyl) being substituted for $-CH_3$). In some embodiments, alkyl groups of the disclosed Formulas (e.g., Formula I) can be perdeuterated.

One or more constituent atoms of the compounds presented herein can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound presented herein can be replaced or substituted by deuterium (*e.g.*, one or more hydrogen atoms of a C_{1-6} alkyl group can be replaced by deuterium atoms, such as $-CD_3$ being substituted for $-CH_3$). In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1-2, 1-3, 1-4, 1-5, 1-6, 1-8, 1-10, 1-12, 1-14, 1-16, 1-18, or 1-20 deuterium atoms. In some embodiments, all of the hydrogen atoms in a compound can be replaced or substituted by deuterium atoms.

In some embodiments, each hydrogen atom of the compounds provided herein, such as hydrogen atoms attached to carbon atoms of alkyl, alkenyl, alkynyl, aryl, phenyl, cycloalkyl, heterocycloalkyl, or heteroaryl substituents or -C_{1-4} alkyl-, alkylene, alkenylene, and alkynylene linking groups, as described herein, is optionally replaced by deuterium atoms.

In some embodiments, each hydrogen atom of the compounds provided herein, such as hydrogen atoms to carbon atoms of alkyl, alkenyl, alkynyl, aryl, phenyl, cycloalkyl, heterocycloalkyl, or heteroaryl substituents or -C_{1-4} alkyl-, alkylene, alkenylene, and alkynylene linking groups, as described herein, is replaced by deuterium atoms (*i.e.*, the alkyl, alkenyl, alkynyl, aryl, phenyl, cycloalkyl, heterocycloalkyl, or heteroaryl substituents, or -C_{1-4} alkyl-, alkylene, alkenylene, and alkynylene linking groups are perdeuterated).

In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 hydrogen atoms, attached to carbon atoms of alkyl, alkenyl, alkynyl, aryl, phenyl, cycloalkyl, heterocycloalkyl, or heteroaryl substituents or -C_{1-4} alkyl-, alkylene, alkenylene, and alkynylene linking groups, as described herein, are optionally replaced by deuterium atoms.

In some embodiments, 1, 2, 3, 4, 5, 6, 7, or 8 hydrogen atoms, attached to carbon atoms of alkyl, alkenyl, alkynyl, aryl, phenyl, cycloalkyl, heterocycloalkyl, or

heteroaryl substituents or -C_{1-4} alkyl-, alkylene, alkenylene and alkynylene linking groups, as described herein, are optionally replaced by deuterium atoms.

In some embodiments, the compound provided herein (*e.g.*, the compound of any of Formulas I-V), or a pharmaceutically acceptable salt thereof, comprises at least one deuterium atom.

In some embodiments, the compound provided herein (*e.g.*, the compound of any of Formulas I-V), or a pharmaceutically acceptable salt thereof, comprises two or more deuterium atoms.

In some embodiments, the compound provided herein (*e.g.*, the compound of any of Formulas I-V), or a pharmaceutically acceptable salt thereof, comprises three or more deuterium atoms.

In some embodiments, for a compound provided herein (*e.g.*, the compound of any of Formulas I-V), or a pharmaceutically acceptable salt thereof, all of the hydrogen atoms are replaced by deuterium atoms (*i.e.*, the compound is "perdeuterated").

Synthetic methods for including isotopes into organic compounds are known in the art (Deuterium Labeling in Organic Chemistry by Alan F. Thomas (New York, N.Y., Appleton-Century-Crofts, 1971; The Renaissance of H/D Exchange by Jens Atzrodt, Volker Derdau, Thorsten Fey and Jochen Zimmermann, Angew. Chem. Int. Ed. 2007, 7744-7765; The Organic Chemistry of Isotopic Labelling by James R. Hanson, Royal Society of Chemistry, 2011). Isotopically labeled compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

Substitution with heavier isotopes, such as deuterium, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. (see *e.g.*, A. Kerekes et. al. J. *Med. Chem.* 2011, 54, 201-210; R. Xu et. al. J. *Label Compd. Radiopharm.* 2015, 58, 308-312). In particular, substitution at one or more metabolism sites may afford one or more of the therapeutic advantages.

The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example,

for *in vitro* V617F labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I, ^{131}I or ^{35}S can be useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br can be useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments, the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I, ^{35}S and ^{82}Br.

The present disclosure can further include synthetic methods for incorporating radio-isotopes into compounds of the disclosure. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of disclosure.

A labeled compound of the disclosure can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind V617F by monitoring its concentration variation when contacting with V617F, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to V617F (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to V617F directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

Kits

The present disclosure also includes pharmaceutical kits useful, for example, in the treatment or prevention of V617F-associated diseases or disorders as described herein, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the disclosure. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with

one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

Preparatory LC-MS purifications of some of the compounds prepared were performed on Waters mass directed fractionation systems. The basic equipment setup, protocols, and control software for the operation of these systems have been described in detail in the literature (see *e.g.* "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Combi. Chem.*, 4, 295 (2002); "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", K. Blom, R. Sparks, J. Doughty, G. Everlof, T. Haque, A. Combs, *J. Combi. Chem.*, 5, 670 (2003); and "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Combi. Chem.*, 6, 874-883 (2004)).

The compounds separated were typically subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity analysis under the following conditions: Instrument = Agilent 1100 series, LC/MSD; Column: Waters Sunfire™ C_{18} 5 μm, 2.1 x 50 mm, Buffers: mobile phase A: 0.025% TFA in water and mobile phase B: acetonitrile; gradient 2% to 80% B in 3 minutes with flow rate 2.0 mL/minute.

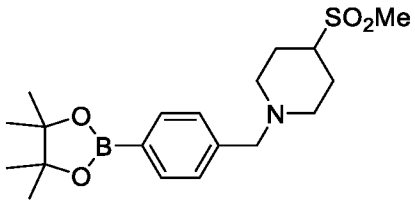
Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-phase high performance liquid chromatography (RP-HPLC)

column conditions are as follows:

pH = 2 purifications: Waters Sunfire™ C_{18} 5 μm, 30 x 100 mm or Waters XBridge™ C_{18} 5 μm, 30 x 100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: acetonitrile; the flow rate was 60 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature (see *e.g.*, "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)).

pH = 10 purifications: Waters XBridge™ C_{18} 5 μm, 30 x 100 mm column, eluting with mobile phase A: 0.1% NH_4OH in water and mobile phase B: acetonitrile; the flow rate was 60 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature (see *e.g.*, "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)).

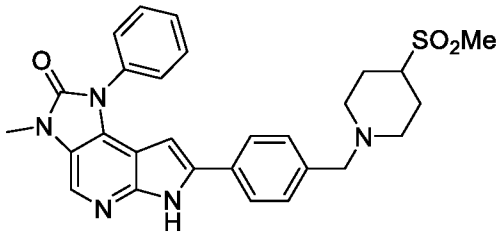
Intermediate 1. 4-(Methylsulfonyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine



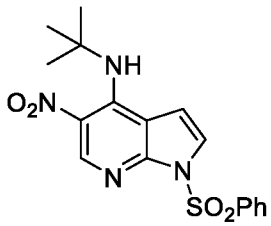
A solution of 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (900 mg, 3.03 mmol) [Sigma-Aldrich, 718513] and 4-(methylsulfonyl)piperidine (700 mg, 4.29 mmol) in dry THF (15 mL) was treated with potassium cesium carbonate (2.00 g, 6.14 mmol) at room temperature followed by stirring at room temperature for 30 minutes. The reaction mixture was then filtered and diluted with ethyl acetate (50 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford

a white, amorphous solid (1.06 g, 2.80 mmol, 93.3%). The product was used without further purification. LCMS for $C_{19}H_{31}BNO_4S$ $(M+H)^+$: m/z = 380.2; Found: 380.2.

Example 1. 3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

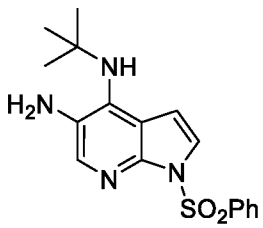


Step 1. N-(tert-Butyl)-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-amine



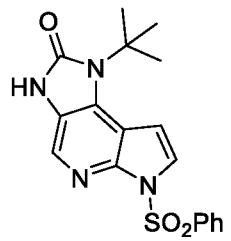
A solution of 4-chloro-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 14.8 mmol) [eNovation Chemicals, D572641] in isopropyl alcohol (40 mL) at room temperature was treated with *tert*-butyl amine (2.50 g, 34.2 mmol) and stirred at 80°C for 30 minutes. The reaction mixture was then cooled to 0°C and maintained at 0°C for 6 hours. The resulting precipitate was collected using filtration followed by washing with hexanes to afford the desired product as a light yellow solid (4.66 g, 12.5 mmol, 84.1%). LCMS for $C_{17}H_{19}N_4O_4S$ $(M+H)^+$: m/z = 375.1; Found: 375.1. ^{1}H NMR (500 MHz, DMSO) δ 8.93 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 2H), 7.83 (d, *J* = 4.2 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 4.2 Hz, 1H), 3.32 (s, 1H), 1.55 (s, 9H).

Step 2. N^4-(tert-Butyl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine



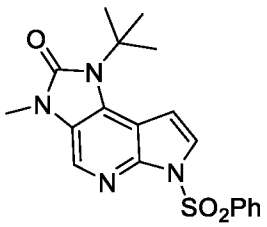
A solution of *N*-(*tert*-butyl)-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (4.50 g, 12.0 mmol) in THF/MeOH/H_2O (1:1:1, 60 mL) was treated with iron powder (4.50 g, 80.5 mmol) and ammonium chloride (4.50 g, 84.9 mmol) at room temperature. The reaction mixture was then stirred at 70°C for 2 hours. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate (200 mL) and water (50 mL), followed by filtration. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark amorphous solid (4.12 g, 99.7%). The crude product was used in the next step without further purification. LCMS for $C_{17}H_{21}N_4O_2S$ $(M+H)^+$: m/z = 345.1; Found: 345.1.

Step 3. 1-(tert-Butyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



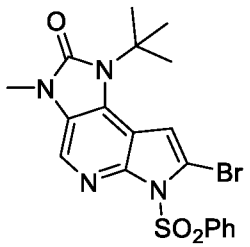
A solution of crude N^4-(*tert*-butyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-4,5-diamine (4.12 g, 12.0 mmol) in dry acetonitrile (80 mL) was treated with 1,1′-carbonyldiimidazole (4.50 g, 27.8 mmol) at room temperature, followed by stirring for 12 hours at the same temperature. The resulting mixture was then diluted with ethyl acetate (500 mL), THF (100 mL), and water (200 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark amorphous solid (4.35 g, 97.9%). The crude product was used in the next step without further purification. LCMS for $C_{18}H_{19}N_4O_3S$ $(M+H)^+$: m/z = 371.1; Found: 371.1.

Step 4. 1-(tert-Butyl)-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of crude 1-(*tert*-butyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (4.35 g, 11.8 mmol) in dry dimethylformamide (80 mL) was treated with 60% NaH in mineral oil (0.80 g, 20.0 mmol) at 0°C, followed by stirring for 30 minutes at 0°C. The resulting mixture was treated with MeI (3.00 g, 21.1 mmol) at 0°C, and stirred for 30 minutes at 0°C. The reaction was quenched with water (20 mL) at 0°C, and diluted with ethyl acetate (500 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark amorphous solid. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (2.91 g, 64.2%). LCMS for $C_{19}H_{21}N_4O_3S$ $(M+H)^+$: m/z = 385.1; Found: 385.1. ^1H NMR (500 MHz, DMSO) δ 8.22 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 2H), 7.98 (d, *J* = 4.2 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 4.2 Hz, 1H), 3.33 (s, 3H), 1.74 (s, 9H).

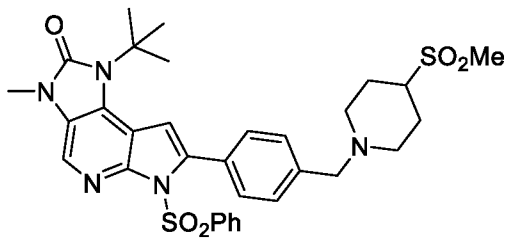
Step 5. 7-Bromo-1-(tert-butyl)-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 1-(*tert*-butyl)-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one (1.46 g, 3.79 mmol) in dry THF (15 mL) was treated with lithium diisopropylamide solution (2.5 mL, 5.0 mmol, 2 M in THF/heptane/ethylbenzene; Sigma-Aldrich, 361798) at -78°C under a nitrogen

atmosphere. The reaction mixture was stirred at -78°C for 30 minutes, and 1,2-dibromotetrachloroethane (2.00 g in 2.00 mL of THF, 6.22 mmol) was then added. The reaction mixture was stirred at -78°C for 30 minutes and then quenched with 5 mL of saturated aqueous NH_4Cl. The resulting mixture was diluted with ethyl acetate (100 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a yellow amorphous solid. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (1.15 g, 2.49 mmol, 65.6%). LCMS for $C_{19}H_{20}BrN_4O_3S$ $(M+H)^+$: m/z = 463.0, 465.0; Found: 463.1, 465.1. ^1H NMR (500 MHz, DMSO) δ 8.21 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 2H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 2H), 7.15 (s, 1H), 3.33 (s, 3H), 1.68 (s, 9H).

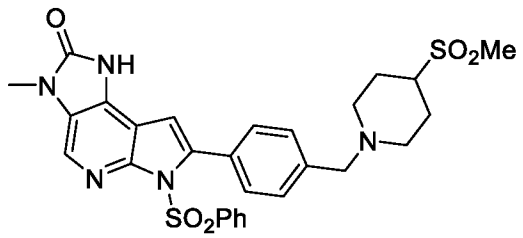
Step 6. 1-(tert-Butyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 7-bromo-1-(*tert*-butyl)-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (150.0 mg, 324.7 µmol) and 4-(methylsulfonyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (Intermediate 1, 190.0 mg, 500.0 µmol) in 1,4-dioxane/water (5:1, 6 mL) was treated with potassium carbonate (100 mg, 724.5 µmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (25 mg, 31.0 µmol) at room temperature followed by stirring at 100 °C for 30 minutes. The reaction mixture was diluted with methanol (25 mL), filtered, and concentrated. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (187.0 mg, 294.5 µmol, 90.7%). LCMS for $C_{32}H_{38}N_5O_5S_2$ $(M+H)^+$: m/z = 636.2; Found: 636.2. ^1H NMR (500 MHz, DMSO) δ 8.22 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 7.8 Hz,

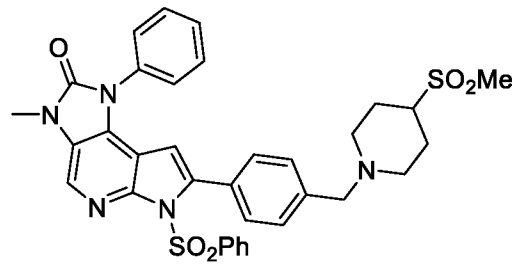
2H), 7.70 – 7.62 (m, 3H), 7.56 (t, *J* = 7.8 Hz, 2H), 6.89 (s, 1H), 4.45 (s, 2H), 3.60 (d, *J* = 11.7 Hz, 2H), 3.45 (t, *J* = 11.7 Hz, 1H), 3.34 (s, 3H), 3.08 (t, *J* = 11.7 Hz, 2H), 3.02 (s, 3H), 2.31 (d, *J* = 11.7 Hz, 2H), 2.00 – 1.83 (m, 2H), 1.72 (s, 9H).

Step 7. 3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 1-(*tert*-butyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (187.0 mg, 294.5 μmol) in TFA (4.00 mL) was stirred at 110°C for 10 hours. The resulting mixture was concentrated and used in the next step without further purification (162.0 mg, 93.8%). LCMS for $C_{28}H_{30}N_5O_5S_2$ $(M+H)^+$: m/z = 580.2; Found: 580.1. ^{1}H NMR (500 MHz, DMSO) δ 9.67 (s, 1H), 8.17 (s, 1H), 7.78-7.72 (m, 4H), 7.66-7.59 (m, 3H), 7.51 (t, *J* = 7.8 Hz, 2H), 6.69 (s, 1H), 4.44 (s, 2H), 3.60 (d, *J* = 11.7 Hz, 2H), 3.45 (t, *J* = 11.7 Hz, 1H), 3.34 (s, 3H), 3.08 (m, 2H), 3.02 (s, 3H), 2.30 (d, *J* = 11.7 Hz, 2H), 2.00 – 1.83 (m, 2H), 1.72 (s, 9H).

Step 8. 3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (162.0 mg, 279.7 μmol) and phenylboronic acid (122.0 mg, 1000.0 μmol) in dichloromethane/triethylamine (3:1, 4 mL) was treated with $Cu(OAc)_2$ (55 mg, 300.0 μmol) at room temperature, followed by stirring at room temperature for 3 hours. The

reaction mixture was diluted with methanol (25 mL), filtered, and concentrated. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (98.0 mg, 149.6 μmol, 53.5%). LCMS for $C_{34}H_{34}N_5O_5S_2$ $(M+H)^+$: m/z = 656.2; Found: 656.2. ^{1}H NMR (500 MHz, DMSO) δ 8.36 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.70 – 7.49 (m, 12H), 5.86 (s, 1H), 4.45 (s, 2H), 3.58 (d, *J* = 10.6 Hz, 2H), 3.48 (s, 3H), 3.46 – 3.36 (m, 1H), 3.12 – 3.02 (m, 2H), 3.00 (s, 3H), 2.28 (d, *J* = 10.6 Hz, 2H), 1.96 – 1.79 (m, 2H).

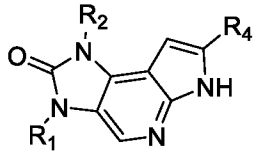
Step 9. 3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

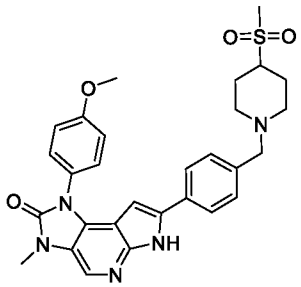
A solution of 3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (90.0 mg, 137.4 μmol) in MeOH (2 mL) was treated with sodium hydroxide (0.3 mL, 0.9 mmol, 3 M in water), and the reaction mixture was stirred at 60°C for 1 hour. The resulting mixture was diluted with MeOH (2 mL) and acidified with TFA (0.2 mL). The mixture was then purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to afford the desired product (55.7 mg, 64.0%) as a TFA salt, a white solid. LCMS for $C_{28}H_{30}N_5O_3S$ $(M+H)^+$: m/z = 516.2; Found: 516.2. ^{1}H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 8.30 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.72 – 7.48 (m, 7H), 6.16 (s, 1H), 4.34 (s, 2H), 3.55 (d, *J* = 11.9 Hz, 2H), 3.51 (s, 3H), 3.40 (t, *J* = 11.9 Hz, 1H), 3.05 – 2.93 (m, 2H), 3.00 (s, 3H), 2.25 (d, *J* = 10.6 Hz, 2H), 1.96 – 1.79 (m, 2H).

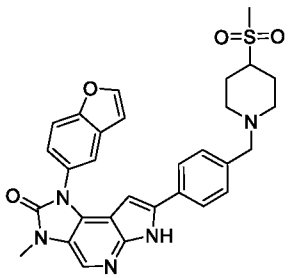
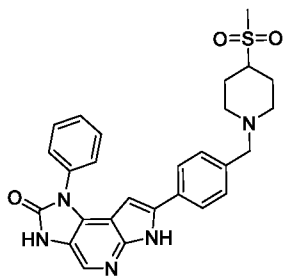
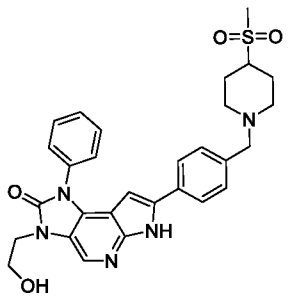
Examples 2-9.

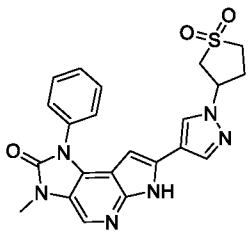
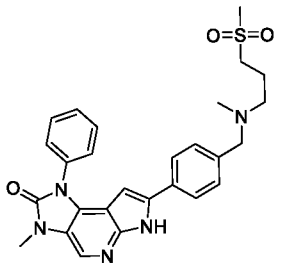
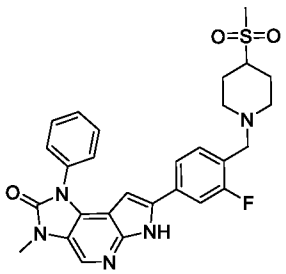
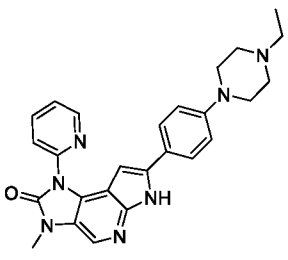
Examples 2-9 in Table 2 were prepared according to the procedures described in Example 1, using appropriately substituted starting materials.

Table 2.

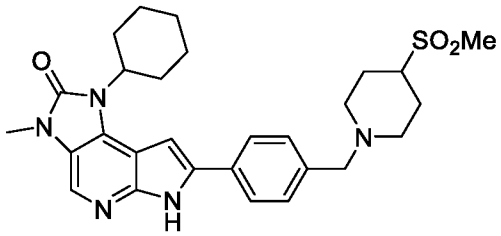


Ex. No.	Name	Structure	LCMS [M+H]+	^{1}H NMR
2	1-(4-Methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		546.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.37 (s, 1H), 8.27 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.58 – 7.51 (m, 4H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.18 (s, 1H), 4.34 (s, 2H), 3.90 (s, 3H), 3.55 (d, *J* = 11.9 Hz, 2H), 3.51 (s, 3H), 3.40 (t, *J* = 11.9 Hz, 1H), 3.05 – 2.93 (m, 2H), 3.00 (s, 3H), 2.25 (d, *J* = 10.6 Hz, 2H), 1.85 (m, 2H).

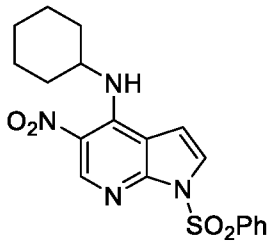
Ex. No.	Name	Structure	LCMS [M+H]+	^{1}H NMR
3	1-(Benzofuran-5-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1*H*)-one		556.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.37 (s, 1H), 8.30 (s, 1H), 8.19 (s, 1H), 7.93 (s, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.57 – 7.48 (m, 3H), 7.13 (s, 1H), 6.10 (s, 1H), 4.34 (s, 2H), , 3.53 (m, 2H), 3.53 (s, 3H), 3.40 (t, *J* = 11.9 Hz, 1H), 3.05 – 2.93 (m, 2H), 3.00 (s, 3H), 2.25 (d, *J* = 10.6 Hz, 2H), 1.85 (m, 2H).
4	7-(4-((4-(Methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		502.2	
5	3-(2-Hydroxyethyl)-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		546.2	

Ex. No.	Name	Structure	LCMS [M+H]+	^{1}H NMR
6	7-(1-(1,1-Dioxidotetrahydrothiophen-3-yl)-1H-pyrazol-4-yl)-3-methyl-1-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		449.1	
7	3-Methyl-7-(4-((methyl(3-(methylsulfonyl)propyl)amino)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		504.2	
8	7-(3-Fluoro-4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3-methyl-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1*H*)-one		534.2	
9	7-(4-(4-Ethylpiperazin-1-yl)phenyl)-3-methyl-1-(pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		454.2	

Example 10. 1-Cyclohexyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

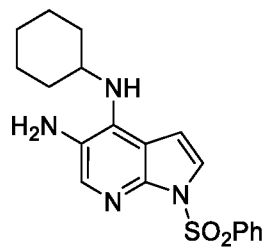


Step 1. N-Cyclohexyl-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-amine



A solution of 4-chloro-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 14.8 mmol; eNovation Chemicals, D572641) in isopropyl alcohol (40 mL) at room temperature was treated with cyclopentyl amine (2.50 g, 29.4 mmol) and stirred at 80°C for 30 minutes. The reaction mixture was cooled to 0°C and maintained at 80°C for 6 hours. The resulting precipitate was collected by filtration, followed by washing with hexanes to afford the desired product as a light yellow solid (4.91 g, 83.1%). LCMS for $C_{19}H_{21}N_4O_4S$ $(M+H)^+$: m/z = 401.1; Found: 401.1. ^{1}H NMR (500 MHz, DMSO) δ 8.90 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 4.2 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 4.2 Hz, 1H), 4.06 (m, 1H), 3.32 (s, 1H), 1.99 (m, 2H), 1.68 (m, 2H), 1.59 (m, 1H), 1.47 (m, 4H), 1.26 (m, 1H).

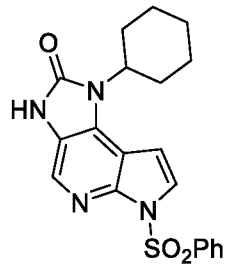
Step 2. N^4-Cyclohexyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine



A solution of *N*-cyclohexyl-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (4.80 g, 12.0 mmol) in THF/MeOH/H_2O (1:1:1, 60 mL) was

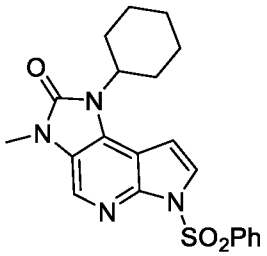
treated with iron powder (4.50 g, 80.5 mmol) and ammonium chloride (4.50 g, 84.9 mmol) at room temperature. The reaction mixture was then stirred at 70°C for 2 hours. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate (200 mL) and water (50 mL), followed by filtration. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a dark amorphous solid (4.21 g, 94.8%). The crude product was used in the next step without further purification. LCMS for $C_{19}H_{23}N_4O_2S$ $(M+H)^+$: m/z = 371.1; Found: 371.2.

Step 3. 1-Cyclohexyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



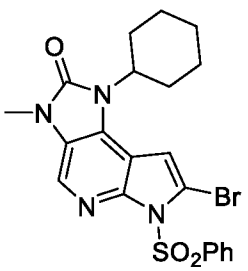
A solution of crude *N*^{4}-cyclohexyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-4,5-diamine (4.21 g, 11.4 mmol) in dry acetonitrile (80 mL) was treated with 1,1′-carbonyldiimidazole (4.50 g, 27.8 mmol) at room temperature, followed by stirring for 12 hours at room temperature. The resulting mixture was diluted with ethyl acetate (500 mL), THF (100 mL) and water (200 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark amorphous solid (4.06 g, 89.9%). The crude product was used in the next step without further purification. LCMS for $C_{20}H_{21}N_4O_3S$ $(M+H)^+$: m/z = 397.1; Found: 397.1.

Step 4. 1-Cyclohexyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of crude 1-cyclohexyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (4.06 g, 10.2 mmol) in dry dimethylformamide (80 mL) was treated with 60% NaH in mineral oil (0.80 g, 20.0 mmol) at 0°C, followed by stirring for 30 minutes. The resulting mixture was treated with MeI (3.00 g, 21.1 mmol) at 0°C, and stirred for 30 minutes. The reaction was quenched with water (20 mL) at 0°C, and diluted with ethyl acetate (500 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a dark amorphous solid. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (2.39 g, 57.1%). LCMS for $C_{21}H_{23}N_4O_3S$ $(M+H)^+$: m/z = 411.1; Found: 411.2. ^{1}H NMR (500 MHz, DMSO) δ 8.21 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 4.2 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 4.2 Hz, 1H), 4.34 (t, *J* = 9.5 Hz, 1 H), 3.37 (s, 3H), 2.14 (m, 2H), 1.84 (d, *J* = 9.5 Hz, 2H), 1.77 (d, *J* = 9.5 Hz, 2H), 1.69 (d, *J* = 11.8 Hz, 1H), 1.48 (m, 2H), 1.28 (m, 1H).

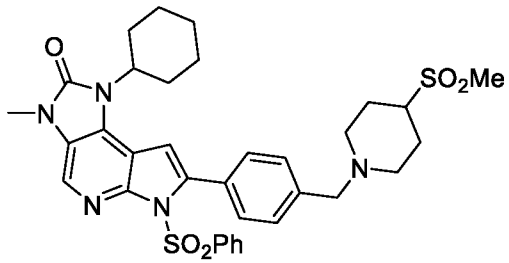
Step 5. 7-Bromo-1-cyclohexyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 1-cyclohexyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (1.60 g, 3.90 mmol) in dry

THF (15 mL) was treated with lithium diisopropylamide solution (2.5 mL, 5.0 mmol, 2 M in THF/heptane/ethylbenzene; Sigma-Aldrich, 361798) at -78°C in a nitrogen atmosphere. The reaction mixture was stirred at -78°C for 30 minutes, then 1,2-dibromotetrachloroethane (2.00 g in 2.00 mL of THF, 6.22 mmol) was added. The reaction mixture was stirred at -78°C for 30 minutes and then quenched with 5 mL of saturated aqueous NH_4Cl. The resulting mixture was diluted with 100 mL of ethyl acetate and 30 mL of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a yellow amorphous solid. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (1.21 g, 63.4%). LCMS for $C_{21}H_{22}BrN_4O_3S$ $(M+H)^+$: m/z = 489.0, 491.0; Found: 489.1, 491.1. ^1H NMR (500 MHz, DMSO) δ 8.20 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.14 (s, 1H), 4.42 (m, 1 H), 3.37 (s, 3H), 2.14 (m, 2H), 1.84 (m, 2H), 1.71 (d, *J* = 9.5 Hz, 2H), 1.69 (m, 1H), 1.52 (m, 2H), 1.28 (m, 1H).

Step 6. 1-Cyclohexyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 7-bromo-1-cyclohexyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (150.0 mg, 306.8 µmol) and 4-(methylsulfonyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (Intermediate 1, 190.0 mg, 500.0 µmol) in dioxane/water (5:1, 6 mL) was treated with potassium carbonate (100 mg, 724.5 µmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (25 mg, 31.0 µmol) at room temperature followed by stirring at 100°C for 30 minutes. The reaction mixture was then diluted with methanol (25 mL), filtered, and concentrated.

Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (162.0 mg, 80.0%). LCMS for $C_{34}H_{40}N_5O_5S_2$ $(M+H)^+$: m/z = 662.2; Found: 662.2. ^{1}H NMR (500 MHz, DMSO) δ 8.21 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 4H), 7.68 – 7.62 (m, 3H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.12 (s, 1H), 4.45 (s, 2H), 4.34 (t, J = 9.6 Hz, 1H), 3.49 – 3.40 (m, 3H), 3.37 (s, 3H), 3.07 (m, 2H), 3.01 (s, 3H), 2.31 (d, *J* = 12.8 Hz, 2H), 2.17 (m, 2H), 1.91 (m, 2H), 1.78 (m, 4H), 1.66 (d, *J* = 12.8 Hz, 1H), 1.48 (m, 2H), 1.21 (m, 1H).

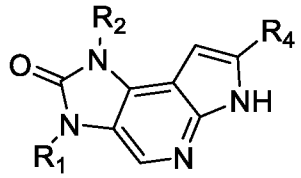
Step 7. 1-Cyclohexyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

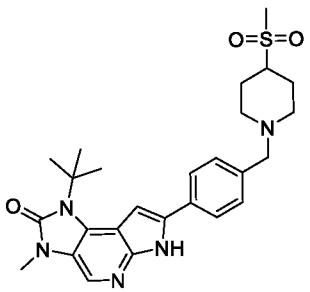
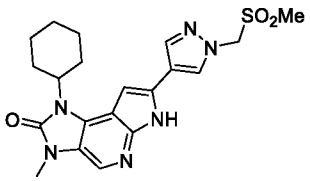
A solution of 1-cyclohexyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (162.0 mg, 249.9 mmol) in MeOH (2 mL) was treated with sodium hydroxide (0.4 mL, 0.9 mmol, 3 M in water) and the reaction mixture was stirred at 60°C for 1 hour. The resulting mixture was diluted with MeOH (2 mL) and acidified with TFA (0.2 mL). The resulting mixture was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to afford the desired product (101.3 mg, 63.8%) as a trifluoroacetic acid salt (a white solid). LCMS for $C_{28}H_{36}N_5O_3S$ $(M+H)^+$: m/z = 522.2; Found: 522.2. ^{1}H NMR (500 MHz, DMSO) δ 12.46 (s, 1H), 8.19 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.23 (s, 1H), 4.49 (t, *J* = 9.6 Hz, 1H), 4.38 (s, 2H), 3.58 (d, *J* = 11.8 Hz, 2H), 3.42 (m, 1H), 3.41 (s, 3H), 3.04 (m, 2H), 3.00 (s, 3H), 2.38 – 2.23 (m, 4H), 1.96 – 1.79 (m, 6H), 1.77 (d, *J* = 12.1 Hz, 1H), 1.59 (m, 2H), 1.36 (m, 1H).

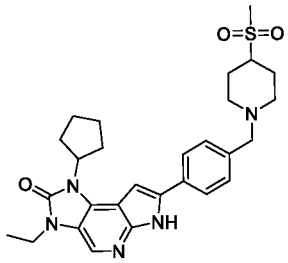
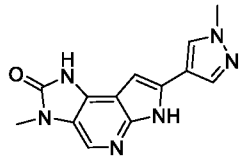
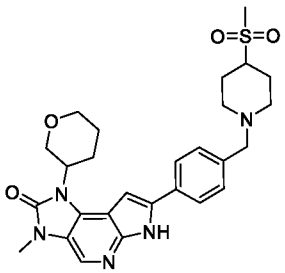
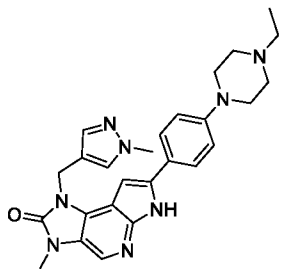
Examples 11-17.

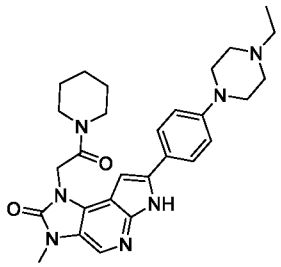
Examples 11-17 in Table 3 were prepared according to the procedures described in Example 10, using appropriately substituted starting materials.

Table 3.

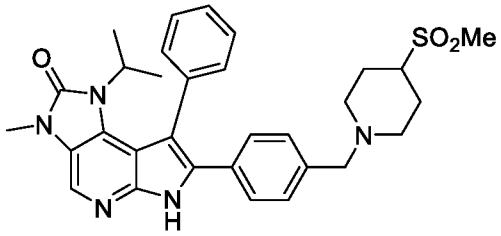


Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
11	1-(*tert*-Butyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		496.2	^1H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 8.19 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.12 (s, 1H), 4.38 (s, 2H), 3.57 (d, *J* = 10.9 Hz, 2H), 3.42 (m, 1H), 3.04 (m, 2H), 3.00 (s, 3H), 2.27 (d, *J* = 10.9 Hz, 2H), 1.90 (m, 2H), 1.86 (s, 9H).
12	1-Cyclohexyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		429.2	^1H NMR (400 MHz, DMSO-d_6) δ δ 12.45 (s, 1H), 8.46 (s, 1H), 8.31 (s, 1H), 8.16 (s, 1H), 6.98 (s, 1H), 4.49 5.86 (s, 2H), 4.46 (t, *J* = 10.0 Hz, 1H), 3.41 (s, 3H), 3.07 (s, 3H), 2.28 (m, 2H), 1.91 (d, *J* = 11.0 Hz, 2H), 1.84 (d, *J* = 11.0 Hz, 2H), 1.75 (d, *J* = 11.7 Hz, 1H), 1.56 (m, 2H), 1.38 (m, 1H).

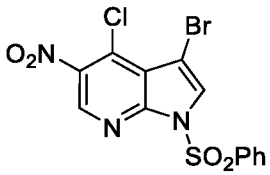
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
13	1-Cyclopentyl-3-ethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		522.3	
14	3-Methyl-7-(1-methyl-1H-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		269.1	
15	3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-(tetrahydro-2H-pyran-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		524.2	
16	7-(4-(4-Ethylpiperazin-1-yl)phenyl)-3-methyl-1-((1-methyl-1*H*-pyrazol-4-yl)methyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		471.3	

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
17	7-(4-(4-Ethylpiperazin-1-yl)phenyl)-3-methyl-1-(2-oxo-2-(piperidin-1-yl)ethyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		502.3	

Example 18. 1-Isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

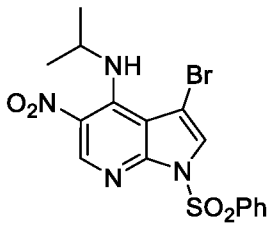


Step 1. 3-Bromo-4-chloro-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine



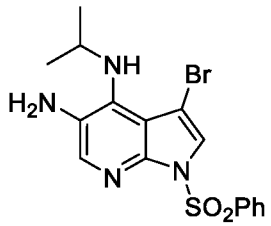
To a solution of 4-chloro-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 14.8 mmol; eNovation Chemicals, D572641) in dry dimethylformamide (30 mL), *N*-bromosuccinimide (5.00 g, 28.1 mmol) was added at room temperature. The resulting mixture was stirred for 60 minutes at 60°C. The yellow reaction mixture was cooled to 0 °C and kept at the same temperature for 6 hours. The resulting precipitate was collected using filtration followed by the wash with hexanes to give the desired product as a light yellow solid (5.35 g, 87.2%). LCMS for $C_{13}H_8BrClN_3O_4S$ $(M+H)^+$: m/z = 415.9, 417.9; Found: 415.9, 417.9. ^1H NMR (500 MHz, DMSO) δ 9.06 (s, 1H), 8.54 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 2H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 2H).

Step 2. 3-Bromo-N-isopropyl-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-amine



A solution of 3-bromo-4-chloro-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 12.0 mmol) in isopropyl alcohol (40 mL) at room temperature was treated with isopropyl amine (2.50 g, 43.3 mmol) and stirred at 80°C for 30 minutes. The yellow reaction mixture was cooled to 0°C and maintained at 0°C for 6 hours. The resulting precipitate was collected via filtration followed by the washing with hexanes to afford the desired product as a light yellow solid (4.51 g, 85.6%). LCMS for $C_{16}H_{16}BrN_4O_4S$ $(M+H)^+$: m/z = 439.0, 441.0; Found: 439.0, 441.0. ^{1}H NMR (500 MHz, DMSO) δ 8.74 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 2H), 8.15 (s, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 2H), 3.86 (m, 1H), 3.31 (s, 1H), 1.19 (d, *J* = 6.3 Hz, 6H).

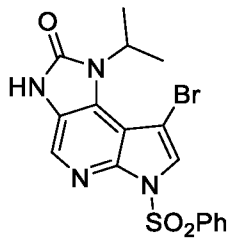
Step 3. 3-Bromo-N^4-isopropyl-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-4,5-diamine



A solution of 3-bromo-*N*-isopropyl-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (4.70 g, 10.7 mmol) in THF/MeOH/H_2O (1:1:1, 60 mL) was treated with iron powder (4.50 g, 80.5 mmol) and amonium chloride (4.50 g, 84.9 mmol) at room temperature. The reaction mixture was stirred at 70°C for 2 hours. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate (200 mL) and water (50 mL), followed by filtration. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark amorphous solid (4.32 g, 98.1%). The crude product was used in the next step without further purification. LCMS for $C_{16}H_{18}BrN_4O_4S$ $(M+H)^+$: m/z = 409.0, 411.0;

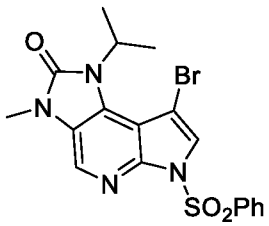
Found: 409.0, 411.0.

Step 4. 8-Bromo-1-isopropyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of crude 3-bromo-N^4-isopropyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-4,5-diamine (4.32 g, 10.5 mmol) in dry acetonitrile (80 mL) was treated with 1,1′-carbonyldiimidazole (4.50 g, 27.8 mmol) at room temperature, followed by stirring for 12 hours. The resulting mixture was diluted with ethyl acetate (500 mL), THF (100 mL), and water (200 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark, amorphous solid (4.19 g, 91.7%) . The crude product was moved to the next step without further purification. LCMS for $C_{17}H_{16}BrN_4O_3S$ $(M+H)^+$: m/z = 435.0, 437.0; Found: 435.0, 437.0.

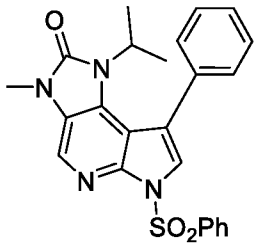
Step 5. 8-Bromo-1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of crude 8-bromo-1-isopropyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (4.19 g, 9.63 mmol) in dry dimethylformamide (80 mL) was treated with 60% NaH in mineral oil (0.80 g, 20.0 mmol) at 0°C, followed by stirring for 30 minutes at 0°C. The resulting mixture was treated with MeI (3.00 g, 21.1 mmol) at 0°C, and stirred at 0°C for 30 minutes. The reaction was quenched with water (20 mL) at 0 °C, and diluted with ethyl acetate (500

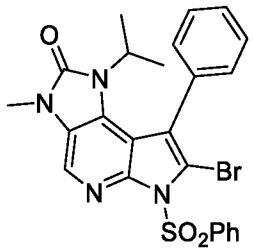
mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark amorphous solid. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (1.82 g, 42.2%). LCMS for $C_{18}H_{18}BrN_4O_3S$ $(M+H)^+$: m/z = 449.0, 451.0; Found: 449.0, 451.0. ^1H NMR (500 MHz, DMSO) δ 8.26 (s, 1H), 8.20 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 2H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 2H), 5.50 (m, 1H), 3.36 (s, 3H), 1.53 (d, *J* = 6.6 Hz, 6H).

Step 6. 1-Isopropyl-3-methyl-8-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



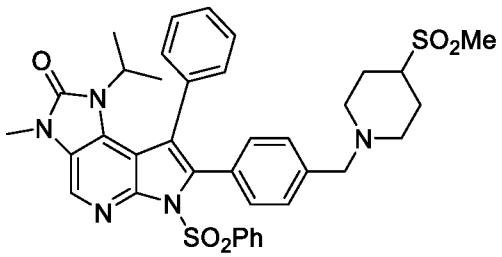
A solution of 8-bromo-1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (0.300 g, 0.668 mmol) and phenylboronic acid (0.122 mmol, 0.100 mmol) in dioxane/water (5:1, 6 mL) was treated with potassium carbonate (0.200 g, 1.449 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (25 mg, 31 μmol) at room temperature followed by stirring at 100 °C for 30 minutes. The reaction mixture was diluted with methanol (20 mL), filtered, and concentrated. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (0.205 g, 68.7%). LCMS for $C_{24}H_{23}N_4O_3S$ $(M+H)^+$: m/z = 447.1; Found: 447.2. ^1H NMR (500 MHz, DMSO) δ 8.25 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 2H), 7.82 (s, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.54 – 7.43 (m, 5H), 3.57 (m, 1H), 3.35 (s, 3H), 1.04 (d, *J* = 6.6 Hz, 6H).

Step 7. 7-Bromo-1-isopropyl-3-methyl-8-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 1-isopropyl-3-methyl-8-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (0.200 g, 0.448 mmol) in dry THF (3 mL) was treated with lithium diisopropylamide solution (0.5 mL, 1.0 mmol, 2 M in THF/heptane/ethylbenzen) [Sigma-Aldrich, 361798] at -78°C in a nitrogen atmosphere. The reaction mixture was stirred at -78°C for 30 minutes before addition of 1,2-dibromotetrachloroethane (0.250 g in 0.5 mL of THF, 0.777 mmol). The reaction mixture was stirred at -78°C for 30 minutes and then quenched by saturated aqueous NH_4Cl (5mL). The resulting mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a yellow amorphous solid. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (0.182 g, 0.345 mmol, 77.0%). LCMS for $C_{24}H_{22}BrN_4O_3S$ $(M+H)^+$: m/z = 525.1, 527.1; Found: 525.0, 527.0. ^1H NMR (500 MHz, DMSO) δ 8.25 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 2H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 2H), 7.58 – 7.50 (m, 3H), 7.41 (d, J = 6.3 Hz, 2H), 3.35 (s, 3H), 3.27 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H).

Step 8. 1-Isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 7-bromo-1-isopropyl-3-methyl-8-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (30.0 mg, 57.1 µmol) and 4-(methylsulfonyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (Intermediate 1, 38.0 mg, 72.4 µmol) in dioxane/water (5:1, 2 mL) was treated with potassium carbonate (20 mg, 144.9 µmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (5 mg, 6.2 µmol) at room temperature followed by stirring at 100°C for 30 minutes. The reaction mixture was diluted with methanol (5 mL), filtered, and concentrated. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (27.0 mg, 38.7 µmol, 52.4%). LCMS for $C_{37}H_{40}N_5O_5S_2$ $(M+H)^+$: m/z = 698.2; Found: 698.3. ^{1}H NMR (500 MHz, DMSO) δ 8.26 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.73 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 8.1 Hz, 2H), 7.54 (d, J = 6.6 Hz, 2H), 7.43 (d, J = 6.6 Hz, 2H), 7.35 – 7.30 (m, 5H), 4.32 (s, 2H), 3.51 (m, 2H). 3.38 (m, 2H), 3.35 (s, 3H), 2.99 (s. 3H), 2.98 (m, 2H), 2.26 (d, *J* = 11.3 Hz, 2H), 1.86 (m, 2H), 0.95 (d, *J* = 6.6 Hz, 6H).

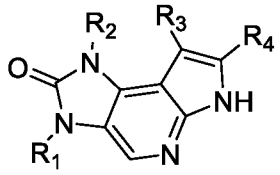
Step 9. 1-Isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

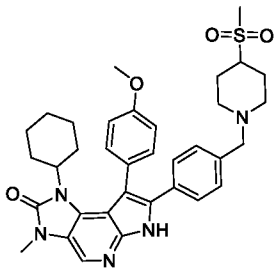
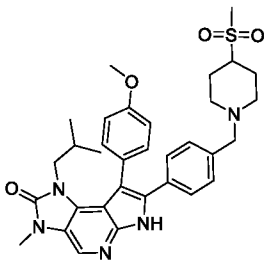
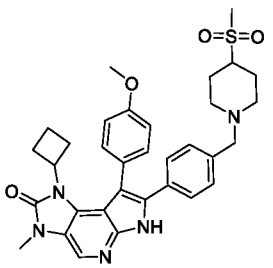
A solution of 1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (27.0 mg, 38.7 µmol) in MeOH (2 mL) was treated with sodium hydroxide (0.3 mL, 0.9 mmol, 3 M in water), and the reaction mixture was stirred at 60 °C for 1 hour. The resulting mixture was diluted with MeOH (2 mL) and acidified with trifluoroacetic acid (TFA, 0.2 mL). The resulting mixture was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% TFA, at flow rate of 60 mL/min) to give the desired product (16.5 mg, 24.6 µmol, 63.6%) as trifluoroacetic acid salt, a white solid. LCMS for $C_{31}H_{36}N_5O_3S$ $(M+H)^+$: m/z = 558.3; Found: 558.3. ^{1}H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 8.23 (s, 1H), 7.55 – 7.37 (m, 9H), 4.25 (s, 2H), 3.51 (d, *J* = 11.3 Hz, 2H). 3.42 (m, 2H), 3.38 (s, 3H), 2.98 (s. 3H), 2.96 (m, 2H), 2.24 (d, *J* = 11.3 Hz, 2H), 1.84 (m, 2H), 1.04 (d, *J* = 6.6 Hz, 6H).

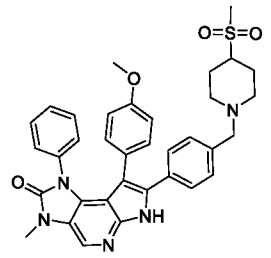
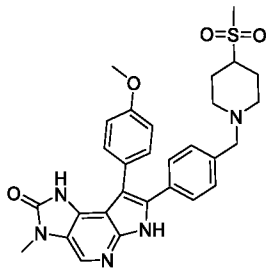
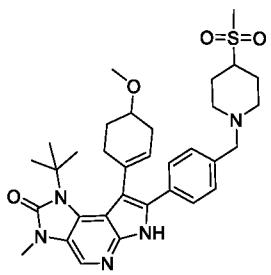
Examples 19-74.

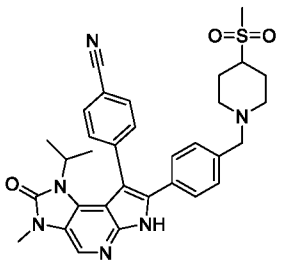
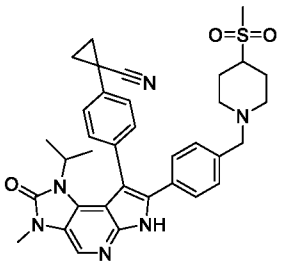
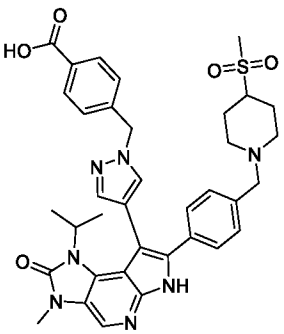
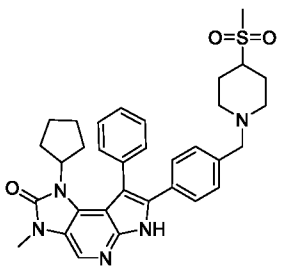
Examples 19-74 in Table 4 were prepared according to the procedures described in Example 18, using appropriately substituted starting materials.

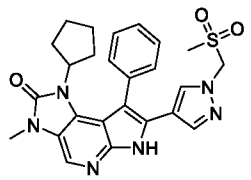
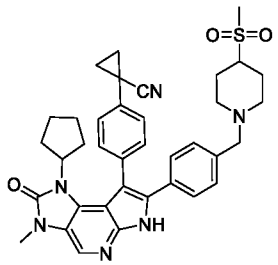
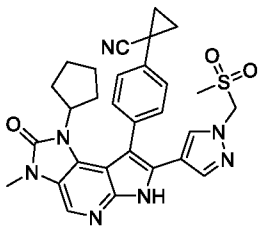
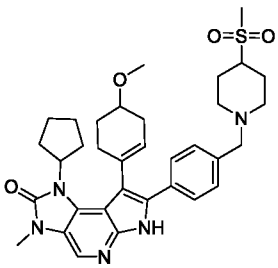
Table 4.

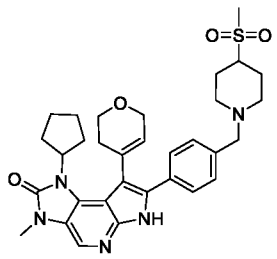
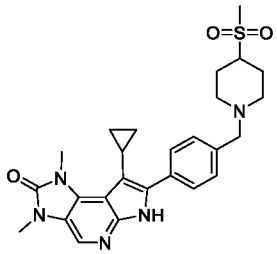
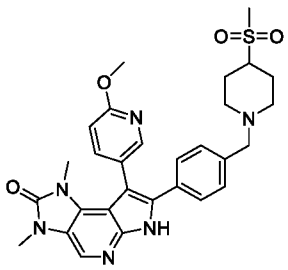
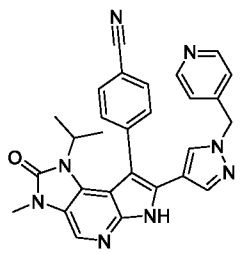


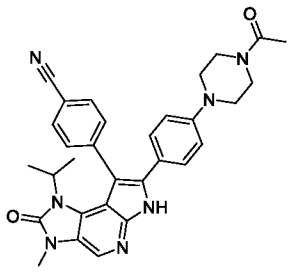
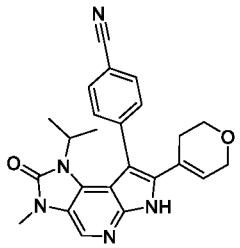
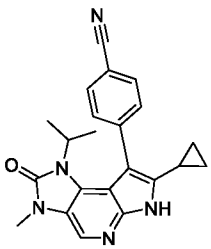
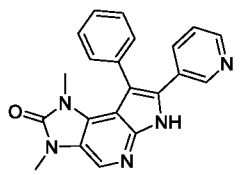
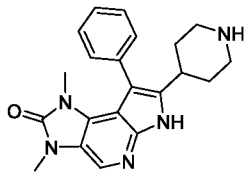
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
19	1-Cyclohexyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		628.3	
20	1-Isobutyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		602.3	
21	1-Cyclobutyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		600.3	

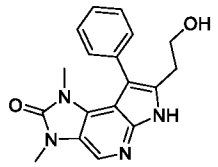
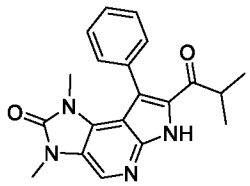
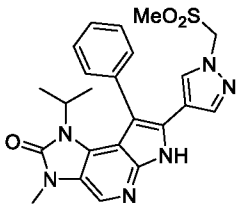
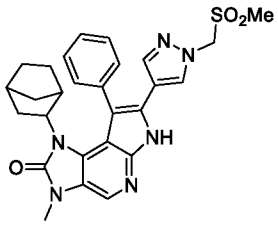
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
22	8-(4-Methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one		622.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.32 (s, 1H), 7.34 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 7.5 Hz, 2H), 7.06 – 6.94 (m ,5H), 6.70 (d, J = 8.5 Hz, 2H), 6.37 (d, J = 8.5 Hz, 2H), 4.23 (s, 2H), 3.71 (s, 3H), 3.49 (s, 3H), 3.46 (m, 1H), 3.38 (m, 2H), 2.99 (s. 3H), 2.97 (m, 2H), 2.23 (d, J = 11.3 Hz, 2H), 1.84 (m, 2H
23	8-(4-Methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		546.2	
24	1-(*tert*-Butyl)-8-(4-methoxycyclohex-1-en-1-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		606.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.09 (s, 1H), 8.00 (m, 1H), 7.72 (d, J = 7.7 Hz, 2H), 7.57 (d, J = 7.7 Hz, 2H), 5.55 (s, 1H), 4.35 (s, 2H), 3.64 – 3.52 (brs, 5H), 3.31 (s, 3H), 3.05 (m, 2H), 3.01 (s, 3H), 2.29 (m, 2H), 2.18 (m, 2H), 2.08 (m, 2H), 1.87 (m, 4H), 1.69 (m, 1H), 1.58 (s, 9H).

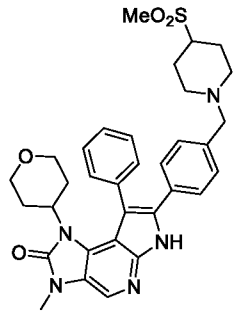
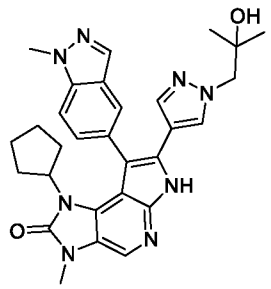
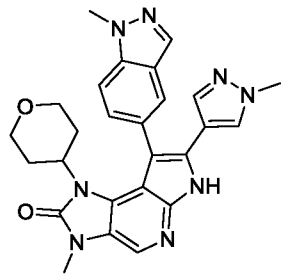
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
25	4-(1-Isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile		583.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 4.27 (s, 2H), 3.57 (m, 4H). 3.38 (s, 3H), 2.99 (s. 3H), 2.97 (m, 2H), 2.24 (d, *J* = 11.3 Hz, 2H), 1.84 (m, 2H), 1.07 (d, *J* = 6.6 Hz, 6H).
26	1-(4-(1-Isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile		623.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.18 (s, 1H), 7.49 – 7.39 (m, 8H), 4.26 (s, 2H), 3.37 (s, 3H), 3.30 – 3.23 (m, 4H), 2.99 (s, 3H), 2.97 (m , 2H) 2.23 (d, *J* = 11.7 Hz, 2H), 1.87 (m, 2H), 1.84 (m, 2H), 1.55 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 6H).
27	4-((4-(1-Isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)-1H-pyrazol-1-yl)methyl)benzoic acid		682.3	
28	1-Cyclopentyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		584.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.22 (s, 1H), 7.55 – 7.36 (m, 9H), 4.25 (s, 2H), 3.41 – 3.34 (m, 4H), 3.38 (s, 3H), 2.96 (s, 3H), 2.97 (m, 2H), 2.23 (d, *J* = 11.7 Hz, 2H), 1.98 (m, 2H), 1.84 (m ,2H), 1.57 (m, 2H), 1.29 (m, 2H), 0.98 (m, 2H).

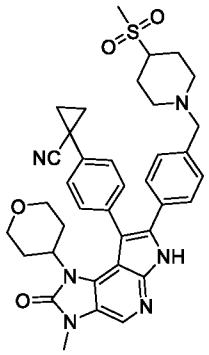
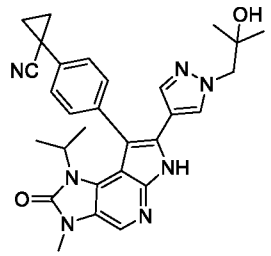
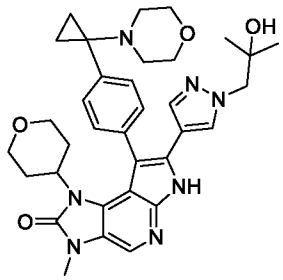
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
29	1-Cyclopentyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		491.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.13 (s, 1H), 7.72 (s, 1H), 7.59 – 7.54 (m, 3H), 7.46 (m, 2H), 7.28 (m, 1H), 5.71 (s, 2H), 3.69 (m, 1H), 3.38 (s, 3H), 2.96 (s, 3H), 1.97 (m, 2H), 1.55 (m, 2H), 1.28 (m, 2H), 0.96 (m, 2H).
30	1-(4-(1-Cyclopentyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile		649.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.17 (s, 1H), 7.53 – 7.26 (m, 8H), 4.24 (s, 2H), 3.58 – 3.41 (m, 4H), 3.39 (s, 3H), 3.37 (m, 2H), 2.99 (s, 3H), 2.97 (m, 2H), 2.23 (m, 2H), 1.99 (m, 2H), 1.87 (m ,2H), 1.60 (m, 2H), 1.55 (m, 2H), 1.27 (m, 2H), 0.96 (m, 2H).
31	1-(4-(1-Cyclopentyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile		556.2	
32	1-Cyclopentyl-8-(4-methoxycyclohex-1-en-1-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		618.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.15 (s, 1H), 8.00 (m, 1H), 7.86 (m, 1H), 7.58 (m, 1H), 7.54 (m, 1H), 5.23 (m, 1H), 4.36 (s, 2H), 3.70 – 3.63 (m, 5H), 3.38 (s, 6H), 3.05 (m, 2H), 2.96 (s, 3H), 2.38 – 2.21 (m, 7H), 2.05 – 1.74 (m, 8H), 1.71 -1.51 (m, 3H)

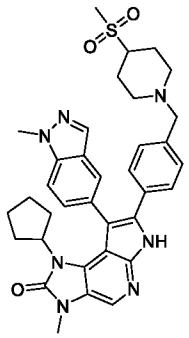
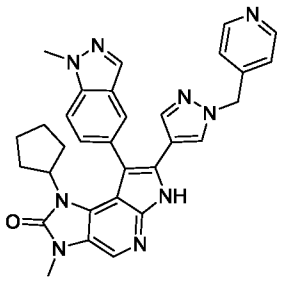
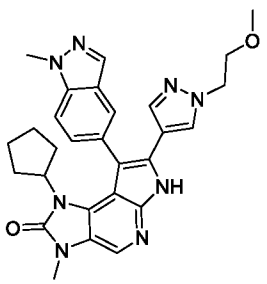
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
33	1-Cyclopentyl-8-(3,6-dihydro-2H-pyran-4-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		590.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.19 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 2H), 6.09 (s, 1H), 5.28 (m, 1H), 4.37 (s, 2H), 3.85 (m, 2H), 3.59 (m, 2H), 3.43 (m, 2H), 3.41 (s, 3H), 3.05 (m, 2H), 3.01 (s, 3H), 2.39 (m, 2H), 2.28 (d, *J* = 10.9 Hz, 2H), 2.15 (m, 3H), 1.95 – 1.82 (m, 6H), 1.66 (m, 2H)
34	8-Cyclopropyl-1,3-dimethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		494.2	
35	8-(6-Methoxypyridin-3-yl)-1,3-dimethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		561.2	
36	4-(1-Isopropyl-3-methyl-2-oxo-7-(1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl)-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile		489.2.	

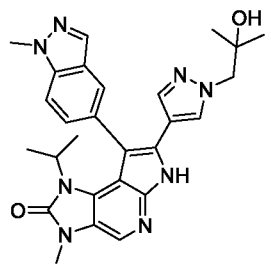
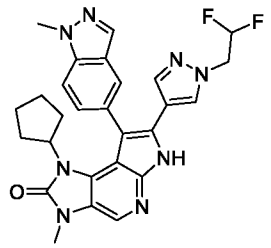
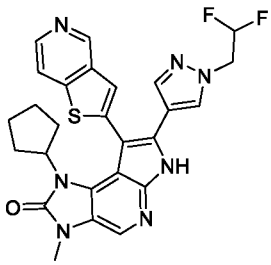
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
37	4-(7-(4-(4-Acetylpiperazin-1-yl)phenyl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile		534.3	
38	4-(7-(3,6-Dihydro-2*H*-pyran-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile		414.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.14 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 5.90 (s, 1H), 4.07 (m, 2H), 3.63 (m, 1H). 3.35 (s, 3H), 3.32 (m, 2H), 2.08 (m, 2H), 1.03 (d, *J* = 6.6 Hz, 6H)
39	4-(7-(3,6-Dihydro-2*H*-pyran-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile		372.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.07 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 3.55 (m, 1H). 3.35 (s, 3H), 1.76 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 6H). 0.94 (m, 2H), 0.89 (m, 2H)
40	1,3-Dimethyl-8-phenyl-7-(pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		356.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 8.57 (s, 1H), 8.58 (s, 1H), 8.50 (d, *J* = 5.5 Hz, 1H), 8.30 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.45 (m, 5H), 3.43 (s, 3H), 2.62 (s, 3H)
41	1,3-Dimethyl-8-phenyl-7-(piperidin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		362.2	

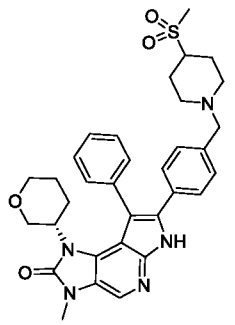
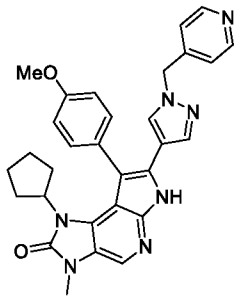
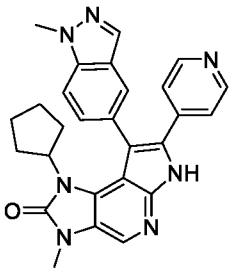
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
42	7-(2-Hydroxyethyl)-1,3-dimethyl-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		323.1	
43	7-Isobutyryl-1,3-dimethyl-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		349.2	
44	1-Isopropyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		465.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.16 (s, 1H), 7.76 (s, 1H), 7.59 – 7.54 (m, 3H), 7.46 (m, 2H), 7.29 (m, 1H), 5.73 (s, 2H), 3.53 (m, 1H), 3.37 (s, 3H), 2.97 (s, 3H), 1.03 (d, J = 6.7 Hz, 6H).
45	1-(Bicyclo[2.2.1]heptan-2-yl)-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		517.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.14 (s, 1H), 7.63 (s, 1H), 7.59 – 7.54 (m, 3H), 7.46 (m, 2H), 7.11 (s, 1H), 5.69 (s, 2H), 3.72 (m, 1H), 3.37 (s, 3H), 2.97 (s, 3H), 2.16 (s, 1H), 2.08 (s, 1H), 1.75 (m, 1H), 1.29 (t, J = 8.9 Hz, 1H). 1.18 (m, 1H), 1.08 (m, 2H), 0.96 (d, J = 9.4 Hz, 1H), 0.39 (m, 1H), 0.29 (m, 1H).

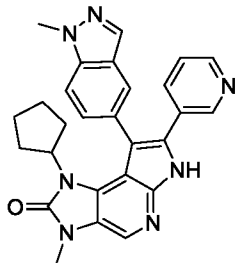
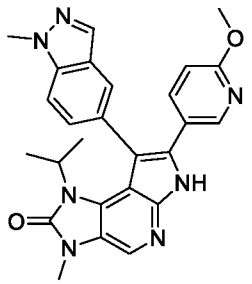
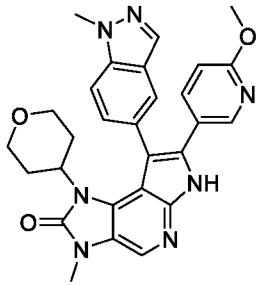
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
46	3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		600.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.24 (s, 1H), 7.55 (m, 3H), 7.48 (m, 2H), 7.36 (m, 4H), 4.25 (s, 2H), 3.64 (d, J = 6.5 Hz, 2H), 3.50 (m, 3H), 3.40 (d, 3H), 3.39 (m, 1H), 2.99 (s, 3H), 2.97 (m, 2H) 2.41 (m, 4H), 2.24 (d, J = 13.1 Hz, 2H), 1.84 (m, 2H), 1.21 (m, 2H)
47	1-Cyclopentyl-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		525.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 8.18 (s, 1H), 8.11 (s, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.83 (s, 1H), 7.59 (s, 1H), 7.42 (d, *J* = 8.9 Hz 1H), 7.09 (s, 1H), 4.12 (s, 3H), 3.87 (s, 2H), 3.51 (m, 1H), 3.36 (s, 3H), 1.96 (m, 1H), 1.83 (m, 1H), 1.41 (m, 1H), 1.29 (m, 1H), 1.22 (m, 1H), 1.07 (m, 1H), 0.95 (s, 6H), 0.60 (m, 1H), 0.14 (m, 1H)
48	3-Methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		483.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 2H), 7.86 (m, 2H), 7.43 (m, 2H), 7.00 (s, 1H), 4.16 (s, 3H), 3.71 (s, 3H), 3.53 (m, 1H), 3.43-3.30 (m, 2H), 3.36 (s, 3H), 2.37 (m, 1H), 2.27 (m, 1H), 1.98 (m, 1H), 1.50 (m, 1H), 1.17 (m, 1H), 1.09 (m, 1H)

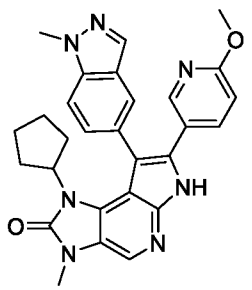
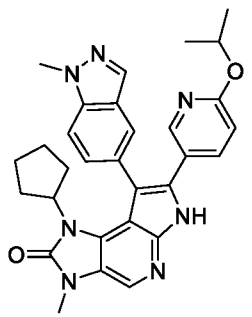
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
49	1-(4-(3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile		665.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.23 (s, 1H), 7.51 – 7.47 (m, 4H), 7.40 (d, *J* = 8.3 Hz 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.25 (s, 2H), 3.69 (m, 2H), 3.50 (m, 2H), 3.42 (m, 2H), 3.39 (s, 3H), 2.99 (s, 3H), 2.97 (m, 2H), 2.42 (m, 2H), 2.34 (m, 2H), 2.25 (m, 2H), 1.90 (m, 2H), 1.85 (m ,2H), 1.56 (m, 2H), 1.22 (m, 2H)
50	1-(4-(7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile		510.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 8.10 (s, 1H), 7.59 (s, 1H), 7.51 (d, *J* = 7.5 Hz 2H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.18 (s, 1H), 3.91 (s, 2H), 3.45 (m, 1H), 3.35 (s, 3H), 1.86 (m, 2H), 1.58 (m, 2H), 1.03 (d, J = 5.7Hz, 6H), 0.99 (s, 6H)
51	7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(4-(1-morpholinocyclopropyl)phenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		612.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.12 (s, 1H), 7.62 (m, 2H), 7.50 (m, 2H), 7.31 (s, 1H), 7.09 (s, 1H), 3.87 (s, 2H), 3.75-3.58 (m, 7H), 3.36 (s, 3H), 2.38 (m, 4H), 2.15 (m, 2H), 1.23 (m, 3H), 1.18-1.07 (m, 2H),1.05-0.95 (m, 3H), 0.99 (s, 6H)

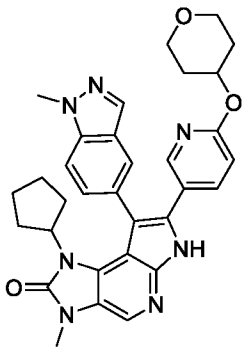
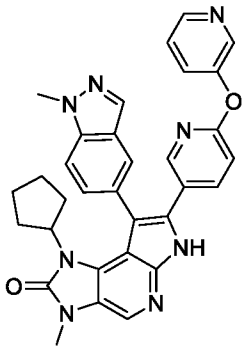
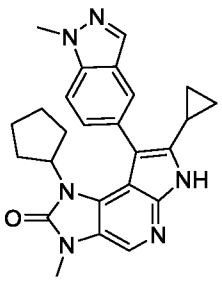
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
52	1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		638.3	^1H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 7.83 (s, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.51 – 7.46 (m, 3H), 7.35 (d, J = 8.3 Hz, 2H), 4.21 (s, 2H), 4.11 (s, 3H), 3.48 (m, 2H), 3.37 (s, 3H), 3.34 (m, 2H), 2.98 (s, 3H), 2.95 (m, 2H), 2.20 (m, 2H), 1,98 (m, 1H), 1.88-1.74 (m, 3H), 1.41 (m ,1H), 1.28 (m, 1H), 1.21 (m, 1H), 1.02 (m, 1H), 0.60 (m, 1H), 0.10 (m, 1H)
53	1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		544.3	
54	1-Cyclopentyl-7-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		511.3	

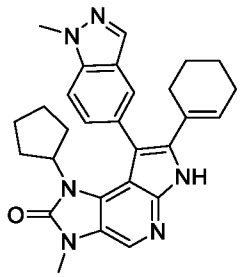
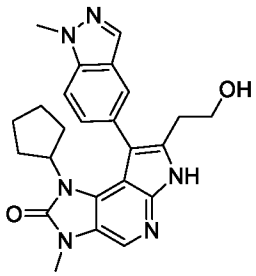
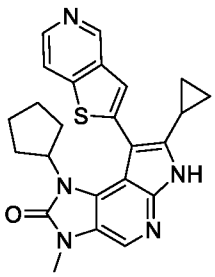
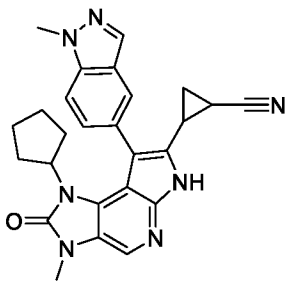
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
55	7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		499.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 8.18 (s, 1H), 8.11 (s, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.83 (s, 1H), 7.59 (s, 1H), 7.42 (d, *J* = 8.9 Hz 1H), 7.04 (s, 1H), 4.14 (s, 3H), 3.87 (s, 2H), 3.51 (m, 1H), 3.36 (s, 3H), 0.96 (d, *J* = 7.4 Hz, 3H), 0.95 (s, 6H), 0.81 d, *J* = 7.4 Hz, 3H)
56	1-Cyclopentyl-7-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		517.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.60 (s, 1H), 7.42 (d, *J* = 8.5 Hz 1H), 7.23 (s, 1H), 4.55 (m, 3H), 4.15 (s, 3H), 3.44 (m, 1H), 3.35 (s, 2H), 1.96 (m, 1H), 1.83 (m, 1H), 1.41 (m, 1H), 1.27 (m, 2H), 1.22 (m, 1H), 1.07 (m, 1H), 0.60 (m, 1H), 0.14 (m, 1H)
57	1-Cyclopentyl-7-(1-(2,2-difluoroethyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(thieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		520.2	

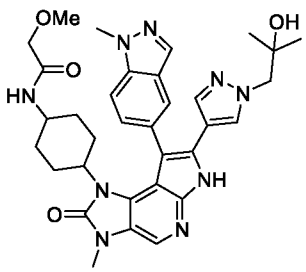
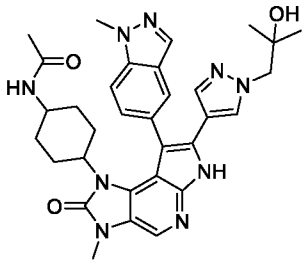
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
58	(*S*)-3-Methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-1-(tetrahydro-2*H*-pyran-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		600.3	
59	1-Cyclopentyl-8-(4-methoxyphenyl)-3-methyl-7-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		520.2	
60	1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyridin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		464.2	^1H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 8.61 (d, J = 6.0 Hz 2H), 8.36 (s, 1H), 8.13 (s, 1H), 7.90 (s, 1H), 7.89 (d, J = 8.2 Hz 1H), 7.62 (d, J = 6.0 Hz, 2H), 7.51(m, 1H), 4.13 (s, 3H), 3.39 (s, 3H), 3.26 (m, 1H), 1.98 (m, 1H), 1.84 (m, 1H), 1.41 (m, 1H), 1.28 (m, 1H), 1.21 (m, 1H), 1.03 (m, 1H), 0.59 (m, 1H), 0.09 (s, 1H)

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
61	1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		464.2	^1H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.58 (m, 1H), 8.46 (m, 1H), 8.28 (s, 1H), 8.09 (s, 1H), 7.88 (m, 1H), 7.86 (s, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.50-7.42 (m, 2H), 4.12 (s, 3H), 3.41 (m, 1H), 3.38 (s, 3H), 1.98 (m, 1H), 1.84 (m, 1H), 1.41 (m, 1H), 1.28 (m, 1H), 1.24 (m, 1H), 1.06 (m, 1H), 0.59 (m, 1H), 0.11 (s, 1H)
62	1-Isopropyl-7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		468.2	
63	7-(6-Methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		510.2	^1H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 8.07 (d, *J* = 2.8 Hz, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.57 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 7.46 (dd, *J* = 8.8 Hz, 1.2 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 4.12 (s, 3H), 3.77 (s, 3H), 3.40 (s, 3H), 3.32 (m, 2H), 2.27 (m, 1H), 2.39 (m, 1H), 1.97 (m, 1H), 1.84 (m, 1H), 1.46 (m, 1H), 1.17 (m, 1H), 1.09 (m, 1H)

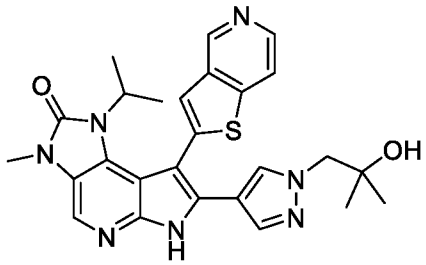
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
64	1-Cyclopentyl-7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		494.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 8.26 (s, 1H), 8.17 (d, *J* = 2.3 Hz, 1H), 8.08 (s, 1H), 7.83 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.66 (dd, *J* = 8.6 Hz, 2.2 Hz, 1H), 7.46 (dd, *J* = 8.6 Hz, 1.5 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 4.10 (s, 3H), 3.78 (s, 3H), 3.41 (m, 1H), 3.39 (s, 3H), 1.98 (m, 1H), 1.84 (m, 1H), 1.41 (m, 1H), 1.28 (m, 1H), 1.24 (m, 1H), 1.06 (m, 1H), 0.59 (m, 1H), 0.11 (s, 1H)
65	1-Cyclopentyl-7-(6-isopropoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		522.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.23 (s, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.86 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.62 (dd, *J* = 7.6 Hz, 2.2 Hz, 1H), 7.45 (dd, *J* = 8.8 Hz, 1.8 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 5.15 (m, 1H), 4.12 (s, 3H), 3.41 (m, 1H), 3.38 (s, 3H), 1.98 (m, 1H), 1.84 (m, 1H), 1.41 (m, 1H), 1.28 (m, 1H), 1.23 (dd, J = 6.4 Hz, 0.9 Hz, 6H), 1.06 (m, 1H), 0.59 (m, 1H), 0.11 (s, 1H)

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
66	1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(6-((tetrahydro-2*H*-pyran-4-yl)oxy)pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		564.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.25 (s, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.66 (dd, *J* = 8.6 Hz, 2.2 Hz, 1H), 7.46 (dd, *J* = 8.6 Hz, 1.5 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 5.08 (m, 1H), 4.10 (s, 3H), 3.81 (m, 2H), 3.47-3.38 (m, 3H), 3.39 (s, 3H), 2.00-1.77 (m, 4H),1.54 (m, 2H), 1.41 (m, 1H), 1.28 (m, 1H), 1.21 (m, 1H), 1.06 (m, 1H), 0.59 (m, 1H), 0.11 (s, 1H)
67	1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(6-(pyridin-3-yloxy)pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		557.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 8.48-8.43 (m, 2H), 8.24 (s, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 8.07 (s, 1H), 7.83 (s, 1H), 7.82 (m, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.66 (m, 1H), 7.53-7.43 (m, 2H), 7.09 (d, *J* = 8.7 Hz, 1H), 4.10 (s, 3H), 3.37 (m, 1H), 3.37 (s, 3H), 1.98 (m, 1H), 1.84 (m, 1H), 1.40 (m, 1H), 1.28 (m, 1H), 1.21 (m, 1H), 1.03 (m, 1H), 0.58 (m, 1H), 0.11 (s, 1H)
68	1-Cyclopentyl-7-cyclopropyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		427.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.09 (s, 2H), 7.81 (s, 1H), 7.76 (d, *J* = 9.1 Hz, 1H), 7.42 (dd, *J* = 9.1 Hz, 0.8 Hz, 1H), 4.12 (s, 3H), 3.54 (m, 1H), 3.34 (s, 3H), 1.98 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.39 (m, 1H), 1.28 (m, 1H), 1.24 (m, 1H), 1.08 (m, 1H), 0.98 (m, 2H), 0.84 (m, 2H), 0.59 (m, 1H), 0.18 (s, 1H)

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
69	7-(Cyclohex-1-en-1-yl)-1-cyclopentyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one		467.3	
70	1-Cyclopentyl-7-(2-hydroxyethyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		431.2	
71	1-Cyclopentyl-7-cyclopropyl-3-methyl-8-(thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-b]pyridin-2(1*H*)-one		430.2	
72	2-(1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)cyclopropane-1-carbonitrile		452.2	

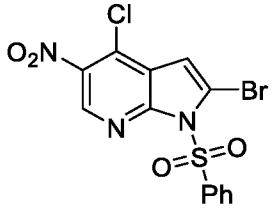
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
73	*N*-(4-(7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)-2-methoxyacetamide		626.3	
74	*N*-(4-(7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2*H*)-yl)cyclohexyl)acetamide		596.3	

Example 75. 7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(thieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one



5

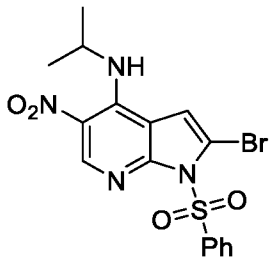
Step 1. 2-Bromo-4-chloro-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine



A solution of 4-chloro-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine

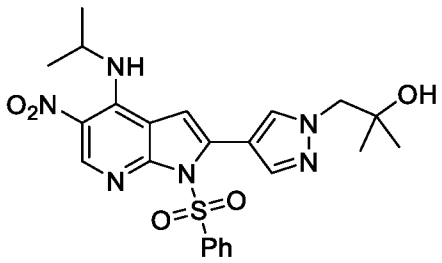
(10.0 g, 29.6 mmol; Affinity) in dichloromethane (100 mL) was stirred with saturated sodium bicarbonate (50 mL) for 10 min. The organic layer was separated, dried with magnesium sulfate, filtered, and concentrated to a yellow solid that was placed under vacuum at reduced pressure at 50 °C for 30 min to give 9.46 g of 4-chloro-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-*b*]pyridine. A solution of 4-chloro-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-*b*]pyridine (9.46 g, 28.0 mmol) in THF (93.0 ml) at -78 °C was treated with LDA (2M solution in THF / heptane / ethylbenzene) (42.0 mL, 84.0 mmol) and stirred at -78 °C for 45 min. The reaction mixture was treated with 1,2-dibromo-1,1,2,2-tetrachloroethane (18.2 g, 56.0 mmol) in THF (93.0 ml) and stirred at -78 °C for 30 min. The reaction mixture was allowed to warm to 0 °C and stirred at 0 °C for 1 h. The reaction mixture was quenched with 1M HCl (100 mL), diluted with water (100 mL), and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to a crude black residue. Purification by flash column chromatography using dichloromethane (100%) gave the desired product (8.64 g, 74.0%) in 50-60% purity. LC/MS for $C_{13}H_8BrClN_3O_4S$ $(M+H)^+$: m/z = 415.9, 417.9; Found: 415.9, 417.9.

Step 2. 2-Bromo-N-isopropyl-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-amine



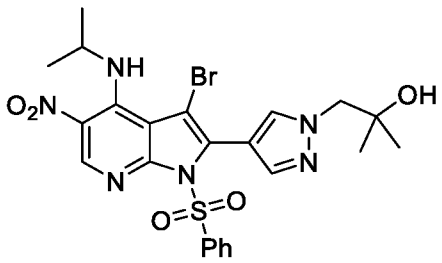
A solution of 2-bromo-4-chloro-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.18 g, 5.24 mmol) and propan-2-amine (0.893 ml, 10.5 mmol) in dichloromethane (30.8 ml) was treated with Hunig's base (2.75 ml, 15.7 mmol) and stirred at 20 °C for 5 h. The reaction mixture was concentrated to give a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 50%) gave the desired product (1.84 g, 80.0%) as a yellow solid. LC/MS for $C_{16}H_{16}BrN_4O_4S$ $(M+H)^+$: m/z = 439.0, 441.0; Found: 439.0, 441.0.

Step 3. 1-(4-(4-(Isopropylamino)-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol



A solution of 2-bromo-*N*-isopropyl-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (1.40 g, 3.19 mmol) and 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propan-2-ol (1.61 g, 6.06 mmol) in 1,4-dioxane (31.9 ml) and water (7.97 ml) was treated with cesium carbonate (4.15 g, 12.8 mmol) and degassed with nitrogen for 5 min. The reaction mixture was treated with dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.416 g, 0.510 mmol), degassed with nitrogen for an additional 5 min, and stirred at 70 °C for 20 h. The reaction mixture was diluted with ethyl acetate (50 mL) and passed through a 0.45 micron filter. The solids were washed with ethyl acetate and the filtrate was washed with brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate [w/ 10% MeOH] in hexanes (0% to 100%) gave the desired product (1.07 g, 67.3%). LC/MS for $C_{23}H_{27}N_6O_5S$ $(M+H)^+$: m/z = 499.2; Found: 499.2.

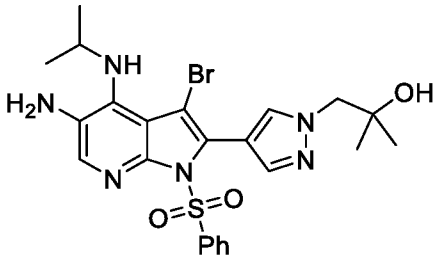
Step 4. 1-(4-(3-Bromo-4-(isopropylamino)-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol



A solution of 1-(4-(4-(isopropylamino)-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-pyrazol-1-yl)-2-methylpropan-2-ol (1.04 g, 2.09 mmol) in dichloromethane (22.0 ml) was treated with bromine (0.215 ml, 4.17 mmol),

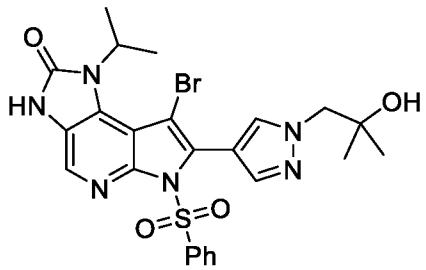
dropwise, and stirred at 20 °C for 15 min. The reaction mixture was cooled to 0 °C and quenched with 10% $Na_2S_2O_3$ in water (10 mL). The ice bath was removed and warmed to 20 °C. The reaction mixture was diluted with dichloromethane (50 mL) and water (20 mL). The aqueous layer was separated and extracted with more dichloromethane (10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate [w/ 5% MeOH] in hexanes (0% to 60%) gave the desired product (1.02 g, 84.6%). LC/MS for $C_{23}H_{26}BrN_6O_5S$ $(M+H)^+$: m/z = 577.1, 579.1; Found: 577.1, 579.1.

Step 5. 1-(4-(5-Amino-3-bromo-4-(isopropylamino)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol



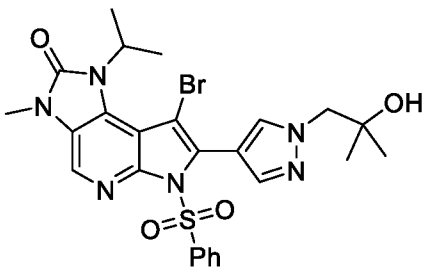
A suspension of 1-(4-(3-bromo-4-(isopropylamino)-5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-pyrazol-1-yl)-2-methylpropan-2-ol (1.02 g, 1.77 mmol) in ethanol (17.7 ml) was treated with tin(II) chloride dihydrate (1.79 g, 7.95 mmol) and stirred at 60 °C for 4 h. The reaction mixture was diluted with 10% potassium carbonate solution (100 mL) and ethyl acetate (75 mL) and stirred for 30 min. The aqueous layer was separated and re-extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the desired product (0.931 g, 96.3%) that was used without further purification. LCMS for $C_{23}H_{28}BrN_6O_3S$ $(M+H)^+$: m/z = 547.1, 549.1; Found: 547.1, 549.2.

Step 6. 8-Bromo-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 1-(4-(5-amino-3-bromo-4-(isopropylamino)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-pyrazol-1-yl)-2-methylpropan-2-ol (0.931 g, 1.70 mmol) in THF (14.2 ml) was treated with 1,1'-carbonyldiimidazole (1.38 g, 8.50 mmol) and stirred at 60 °C for 15 h. The reaction mixture was cooled to 0 °C and quenched with water (10 mL) in portions. The aqueous layer was extracted with ethyl acetate (3x). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the crude mixture. This material was treated with 0.5 M sodium carbonate in water (5 mL) and 1,4-dioxane (5 mL) and stirred at 60 °C for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate (2x). The combined organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate [w/ 10% MeOH] in hexanes (0% to 80%) gave the desired product (0.328 g, 33.6%). LC/MS for $C_{24}H_{26}BrN_6O_4S$ $(M+H)^+$: m/z = 573.1, 575.1; Found: 573.1, 575.1.

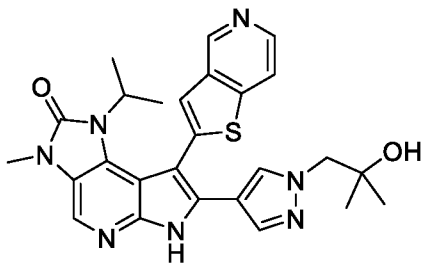
Step 7. 8-Bromo-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of 8-bromo-7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-

one (0.328 g, 0.572 mmol) in DMF (5.72 ml) was treated with cesium carbonate (0.559 g, 1.72 mmol) and stirred at 20 °C for 5 min. The reaction mixture was treated with iodomethane (0.250 ml, 4.00 mmol) and stirred at 20 °C for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic extracts were washed with water (3x), washed with brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate [w/ 10% MeOH] in hexanes (0% to 80%) gave the desired product (0.330 g, 98.2%). LC/MS for $C_{25}H_{28}BrN_6O_4S$ $(M+H)^+$: m/z = 587.1, 589.1; Found: 587.1, 589.1.

Step 8. 7-(1-(2-Hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



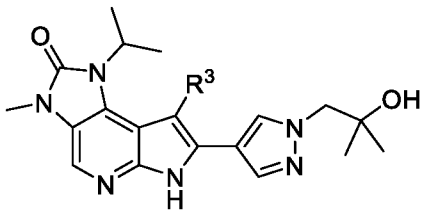
A mixture of 8-bromo-7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one (0.008 g, 0.014 mmol), thieno[3,2-*c*]pyridin-2-ylboronic acid (7.31 mg, 0.041 mmol), and tetrakis(triphenylphosphine)palladium(0) (2.360 mg, 2.043 µmol) in 1,4-dioxane (0.227 mL) and 1.0 N sodium carbonate in water (0.068 mL, 0.034 mmol) was degassed with nitrogen for 5 min, and stirred in a sealed vial at 90 °C for 16 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The filtrate was concentrated to a yellow oil and placed under vacuum at reduced pressure for 30 min. This material was dissolved in methanol (0.60 mL), treated with 3.0 N potassium hydroxide in water (0.272 mL, 0.817 mmol), and stirred at 40 °C for 2 h. The reaction mixture was diluted with trifluoroacetic acid (0.084 mL, 1.089 mmol), followed by methanol and water. This material was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow

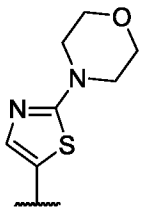
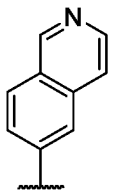
rate of 60 mL/min) to give the desired product (1.4 mg, 13.7%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.56 (s, 1H), 9.50 (s, 1H), 8.71 (d, J = 6.2 Hz, 1H), 8.63 (d, J = 6.1 Hz, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.76 (s, 1H), 7.41 (s, 1H), 3.92 (s, 2H), 3.69 (hept, J = 6.8 Hz, 1H), 3.37 (s, 3H), 1.05 (d, J = 6.8 Hz, 6H), 0.96 (s, 6H). LCMS for $C_{26}H_{28}N_7O_2S$ $(M+H)^+$: m/z = 502.1; Found: 502.1.

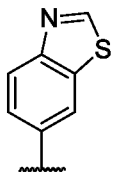
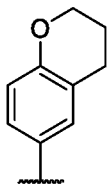
Examples 76-79.

Examples 76-79 in Table 5 were prepared according to the procedures described in Example 88 using appropriately substituted starting materials.

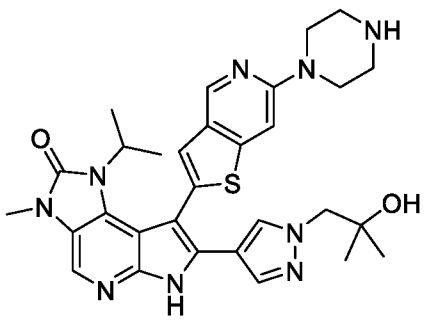
Table 5.



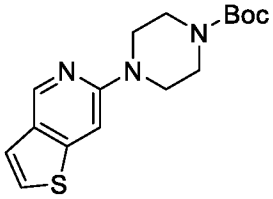
Ex. No.	Name	R^3	LCMS $[M+H]^+$	^{1}H NMR Spectrum
76	7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(2-morpholinothiazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		537.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.10 (s, 1H), 7.86 (s, 1H), 7.55 (s, 1H), 7.22 (s, 1H), 4.21 – 4.10 (m, 1H), 4.00 (s, 2H), 3.78 – 3.71 (m, 4H), 3.47 – 3.40 (m, 4H), 3.36 (s, 3H), 1.29 (s, 6H), 1.04 (s, 6H).
77	7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-8-(isoquinolin-6-yl)-3-methyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		496.3	

Ex. No.	Name	R^3	LCMS $[M+H]^+$	^1H NMR Spectrum
78	8-(Benzo[*d*]thiazol-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		502.2	
79	8-(Chroman-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		501.3	^1H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.09 (s, 1H), 7.64 (s, 1H), 7.26 (s, 1H), 7.13 – 7.06 (m, 2H), 6.93 – 6.86 (m, 1H), 4.22 (t, J = 5.3 Hz, 2H), 3.94 (s, 2H), 3.75 – 3.63 (m, 1H), 3.36 (s, 3H), 2.82 – 2.69 (m, 2H), 2.03 – 1.90 (m, 2H), 1.09 (t, J = 6.4 Hz, 6H), 1.02 (d, J = 2.0 Hz, 6H).

Example 80. 7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(6-(piperazin-1-yl)thieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

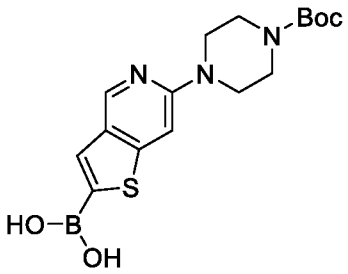


Step 1. tert-Butyl 4-(thieno[3,2-c]pyridin-6-yl)piperazine-1-carboxylate



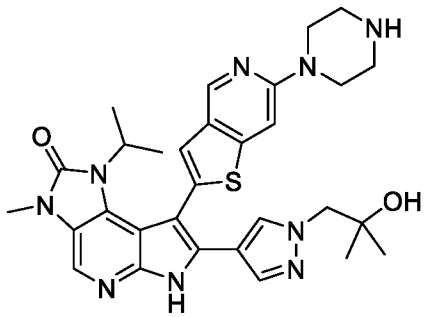
A mixture of 6-chlorothieno[3,2-c]pyridine (0.025 g, 0.147 mmol), *tert*-butyl piperazine-1-carboxylate (0.082 g, 0.442 mmol), and chloro-(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (RuPhos Pd G2) (0.011 g, 0.015 mmol) in 1,4-dioxane (1.47 ml) was degassed with nitrogen for 5 min, treated with sodium tert-butoxide (0.071 g, 0.737 mmol), degassed with nitrogen for an additional 5 min, and stirred at 100 °C for 16 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The filtrate was concentrated to a yellow oil. Purification by flash column chromatography using ethyl acetate [w/ 10% MeOH] in hexanes (0% to 100%) gave the desired product (0.035 g, 74.3%). LC/MS for $C_{16}H_{22}N_3O_2S$ $(M+H)^+$: m/z = 320.1; Found: 320.3.

Step 2. (6-(4-(tert-Butoxycarbonyl)piperazin-1-yl)thieno[3,2-c]pyridin-2-yl)boronic acid



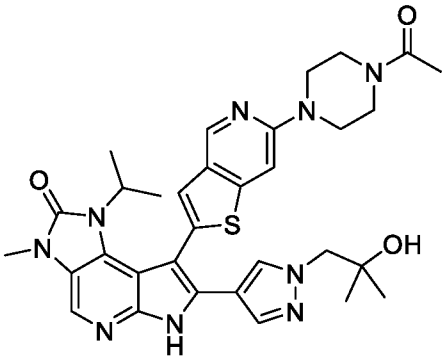
A solution of tert-butyl 4-(thieno[3,2-*c*]pyridin-6-yl)piperazine-1-carboxylate (0.018 g, 0.056 mmol) in THF (0.564 ml) at -78 °C was treated with 1.6 M n-butyllithium in hexanes (0.053 ml, 0.085 mmol) dropwise and stirred at -78 °C for 1 h. The reaction mixture was treated with triisopropyl borate (0.020 ml, 0.085 mmol), stirred at -78 °C for 10 min, and stirred at rt for 75 min. The reaction mixture was diluted with 1.0 N HCl in water (0.085 ml, 0.085 mmol) and water. The mixture was concentrated to a white solid and placed under vacuum at reduced pressure for 6 h to give the desired product that was used immediately without purification. LC/MS for $C_{16}H_{23}BN_3O_4S$ $(M+H)^+$: m/z = 364.1; Found: 364.1.

Step 3. 7-(1-(2-Hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(6-(piperazin-1-yl)thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



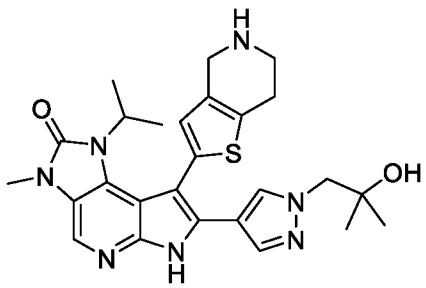
A solution of 8-bromo-7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (0.012 g, 0.020 mmol), tetrakis(triphenylphosphine)palladium(0) (0.004 g, 3.46 μmol), (6-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)thieno[3,2-*c*]pyridin-2-yl)boronic acid (0.020 g, 0.056 mmol) in 1,4-dioxane (0.584 mL) and 1.0 N sodium carbonate in water (0.102 mL, 0.051 mmol) was degassed with nitrogen for 5 min and stirred at 90 °C for 16 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The filtrate was concentrated to a yellow oil and placed under vacuum at reduced pressure for 30 min. This material was dissolved in dichloromethane (0.50 mL) and TFA (0.50 mL) and stirred at rt for 30 min. The reaction mixture was concentrated twice from acetonitrile and placed under vacuum at reduced pressure for 30 min. This material was dissolved in methanol (0.50 mL), treated with 3.0 N potassium hydroxide in water (0.272 mL, 0.817 mmol), and stirred at 40 °C for 90 min. The reaction mixture was diluted with trifluoroacetic acid (0.084 mL, 1.089 mmol) followed by methanol and water. This material was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product (9.8 mg, 58.9%). LCMS for $C_{30}H_{36}N_9O_2S$ $(M+H)^+$: m/z = 586.3; Found: 586.3.

Example 81. 8-(6-(4-Acetylpiperazin-1-yl)thieno[3,2-*c*]pyridin-2-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one



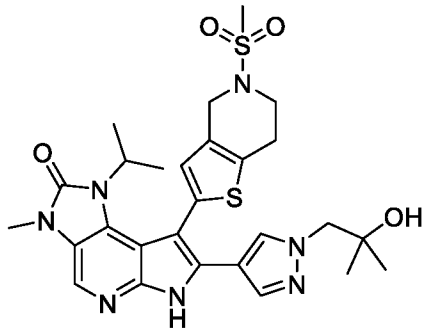
A solution of 7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(6-(piperazin-1-yl)thieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one, TFA (3.90 mg, 5.57 μmol) and acetic acid (1.595 μL, 0.028 mmol) in DMF (0.159 ml) was treated with HATU (2.75 mg, 7.25 μmol), stirred for a few minutes, treated with triethylamine (7.77 μL, 0.056 mmol) and stirred at rt for 30 min. The reaction mixture was diluted with methanol and water and was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product (3.10 mg, 75.1%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.77 (s, 1H), 8.14 (s, 1H), 7.83 (s, 1H), 7.50 (s, 1H), 7.44 (s, 1H), 4.76 (br s, 1H), 4.08 – 3.97 (m, 1H), 3.94 (s, 2H), 3.66 – 3.56 (m, 8H), 3.37 (s, 3H), 2.08 (s, 3H), 1.10 (s, 6H), 0.99 (s, 6H). LCMS for $C_{32}H_{38}N_9O_3S$ $(M+H)^+$: m/z = 628.3; Found: 628.3.

Example 82. 7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one



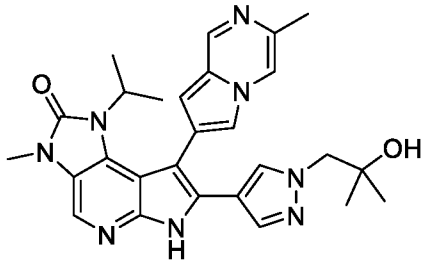
The desired compound was prepared according to the procedure of Example 93, Step 3, using tert-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-carboxylate in place of (6-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)thieno[3,2-c]pyridin-2-yl)boronic acid as the starting material. LCMS for $C_{26}H_{32}N_7O_2S$ $(M+H)^+$: m/z = 506.2; Found: 506.1.

Example 83. 7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(5-(methylsulfonyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

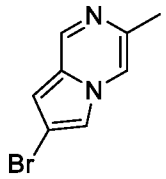


A solution of 7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (0.0035 g, 6.92 μmol) in THF (0.154 ml) and pyridine (0.077 ml) was treated with a solution of methanesulfonyl chloride (0.701 μL, 9.00 μmol) in dichloromethane (0.04 mL) and stirred at rt for 2 h. The reaction mixture was treated with additional methanesulfonyl chloride (0.35 μL, 4.5 μmol) in dichloromethane (0.02 mL) twice. The reaction mixture was diluted with methanol and concentrated to a crude residue. This material was diluted with methanol, water, and a few drops of TFA, and purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product (4.30 mg, 89.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 8.08 (s, 1H), 7.81 (d, J = 0.7 Hz, 1H), 7.41 (d, J = 0.7 Hz, 1H), 7.00 (s, 1H), 4.34 (d, J = 18.0 Hz, 2H), 3.97 (s, 2H), 3.84 – 3.73 (m, 1H), 3.60 – 3.55 (m, 2H), 3.35 (s, 3H), 3.00 (s, 3H), 2.99 – 2.96 (m, 2H), 1.22 (s, 6H), 1.02 (s, 6H). LCMS for $C_{27}H_{34}N_7O_4S_2$ $(M+H)^+$: m/z = 584.2; Found: 584.2.

Example 84. 7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(3-methylpyrrolo[1,2-*a*]pyrazin-7-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

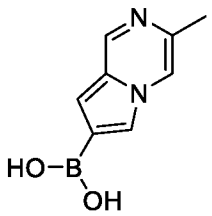


Step 1. 7-Bromo-3-methylpyrrolo[1,2-a]pyrazine



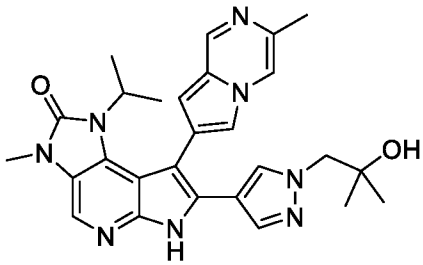
A mixture of 4-bromo-1*H*-pyrrole-2-carbaldehyde (0.100 g, 0.575 mmol) and potassium carbonate (0.119 g, 0.862 mmol) in acetonitrile (2.30 ml) was treated with 1-bromopropan-2-one (0.058 ml, 0.690 mmol) and stirred at rt for 16 h under nitrogen while shielded from light. The reaction mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to a tan film. This material was diluted with acetic acid (2.30 mL), treated with ammonium acetate (0.997 g, 12.9 mmol), and stirred at 120 °C for 3 h. The reaction mixture was cooled to rt and concentrated. The residue was treated with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3x). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to a brown solid. Purification by flash column chromatography using ethyl acetate [w/ 10% MeOH] in hexanes (0% to 100%) gave the desired product (97.0 mg, 80.2%). LC/MS for $C_8H_8BrN_2$ $(M+H)^+$: m/z = 211.0, 213.0; Found: 211.0, 213.0.

Step 2. (3-Methylpyrrolo[1,2-a]pyrazin-7-yl)boronic acid



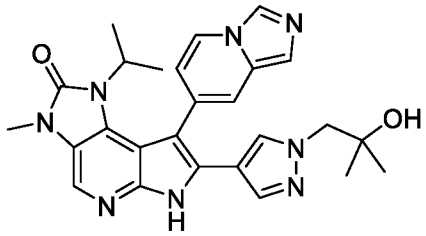
A mixture of 7-bromo-3-methylpyrrolo[1,2-*a*]pyrazine (0.025 g, 0.118 mmol), bis(pinacolato)diboron (0.039 g, 0.154 mmol), and potassium acetate (0.038 g, 0.391 mmol) was degassed with nitrogen for 5 min, treated with dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.015 g, 0.018 mmol), degassed with nitrogen for another 5 min, and stirred at 80 °C for 6 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The filtrate was concentrated to give the desired product that was used without further purification. LC/MS for $C_8H_{10}BN_2O_2$ $(M+H)^+$: m/z = 177.0; Found: 177.0.

Step 3. 7-(1-(2-Hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(3-methylpyrrolo[1,2-a]pyrazin-7-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

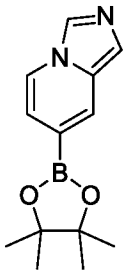


The desired compound was prepared according to the procedure of Example 88, Step 8, using (3-methylpyrrolo[1,2-*a*]pyrazin-7-yl)boronic acid in place of thieno[3,2-*c*]pyridin-2-ylboronic acid as the starting material. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 9.38 (s, 1H), 8.55 (s, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 7.63 (d, *J* = 5.3 Hz, 2H), 7.25 (s, 1H), 3.91 (s, 2H), 3.87 (br s, 1H), 3.47 – 3.36 (m, 1H), 3.35 (s, 3H), 2.50 – 2.45 (m, 3H), 1.03 (d, *J* = 6.7 Hz, 6H), 0.98 (s, 6H). LCMS for $C_{27}H_{31}N_8O_2$ $(M+H)^+$: m/z = 499.3; Found: 499.1.

Example 85. 7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-8-(imidazo[1,5-*a*]pyridin-7-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

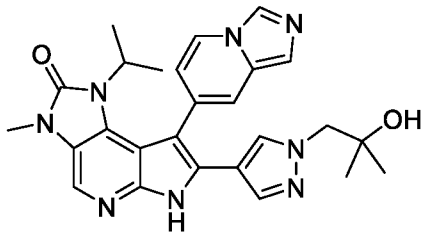


Step 1. 7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,5-a]pyridine



The desired compound was prepared according to the procedure of Example 97, Step 2, using 7-bromoimidazo[1,5-*a*]pyridine in place of 7-bromo-3-methylpyrrolo[1,2-*a*]pyrazine as the starting material. LCMS for $C_{13}H_{18}BN_2O_2$ $(M+H)^+$: m/z = 245.1; Found: 245.2.

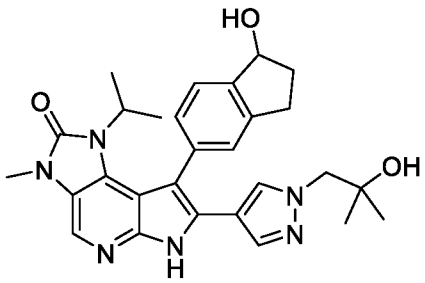
Step 2. 7-(1-(2-Hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-8-(imidazo[1,5-a]pyridin-7-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



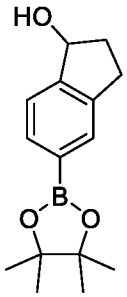
The desired compound was prepared according to the procedure of Example 88, Step 8, using 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,5-*a*]pyridine in place of thieno[3,2-*c*]pyridin-2-ylboronic acid as the starting material. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 9.20 (s, 1H), 8.62 (dt, *J* = 7.2, 1.1 Hz, 1H), 8.11 (s, 1H), 7.82 (s, 2H), 7.74 (d, *J* = 0.8 Hz, 1H), 7.45 (d, *J* = 0.8 Hz, 1H), 6.96 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.04 – 3.93 (m, 1H), 3.92 (s, 2H), 3.35 (s, 3H), 1.16 (d,

J = 6.7 Hz, 3H), 0.97 (s, 9H). LCMS for $C_{26}H_{29}N_8O_2$ $(M+H)^+$: m/z = 485.2; Found: 485.3.

Example 86. 8-(1-Hydroxy-2,3-dihydro-1*H*-inden-5-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

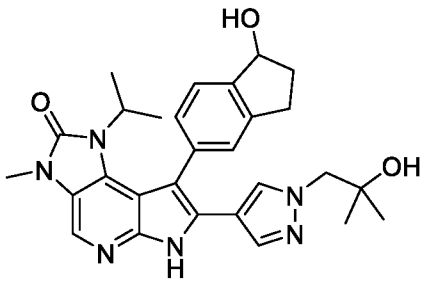


Step 1. 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-ol



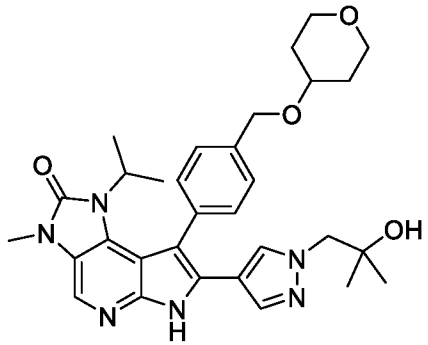
The desired compound was prepared according to the procedure of Example 97, Step 2, using 5-bromo-2,3-dihydro-1*H*-inden-1-ol in place of 7-bromo-3-methylpyrrolo[1,2-*a*]pyrazine as the starting material. LCMS for $C_{15}H_{21}BO_3Na$ $(M+Na)^+$: m/z = 283.2; Found: 283.2.

Step 2. 8-(1-Hydroxy-2,3-dihydro-1H-inden-5-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

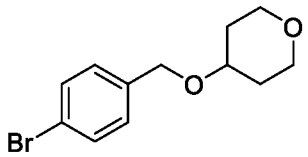


The desired compound was prepared according to the procedure of Example 88, Step 8, using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-1-ol in place of thieno[3,2-*c*]pyridin-2-ylboronic acid as the starting material. LCMS for $C_{28}H_{33}N_6O_3$ $(M+H)^+$: m/z = 501.3; Found: 501.3.

Example 87. 7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4-(((tetrahydro-2*H*-pyran-4-yl)oxy)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

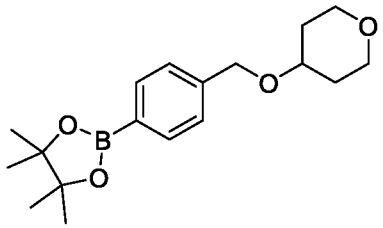


Step 1. 4-((4-Bromobenzyl)oxy)tetrahydro-2H-pyran



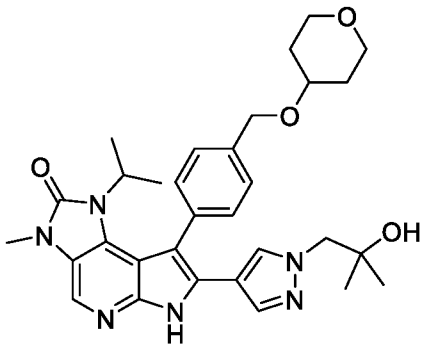
A solution of tetrahydro-2*H*-pyran-4-ol (0.500 g, 4.90 mmol) in DMF (2.45 ml) at 0 °C in an oven dried flask was treated with sodium hydride (60% in oil) (0.235 g, 5.87 mmol) in portions and stirred at rt for 30 min. The reaction mixture was treated with a solution of 1-bromo-4-(bromomethyl)benzene (1.22 g, 4.90 mmol) in DMF (2.27 ml, 29.4 mmol) dropwise and stirred at rt for 14 h. The reaction mixture was cooled to 0 °C, quenched with water (30 ml), and extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to a tan oil. Purification by flash column chromatography using methyl tert-butyl ether in hexanes (0% to 30%) gave the desired product (1.12 g, 84.6%). LC/MS for $C_{12}H_{19}BrNO_2$ $(M+NH_4)^+$: m/z = 288.1, 290.1; Found: 288.1, 290.1.

Step 2. 4,4,5,5-Tetramethyl-2-(4-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)phenyl)-1,3,2-dioxaborolane



A mixture of 4-((4-bromobenzyl)oxy)tetrahydro-2*H*-pyran (0.100 g, 0.369 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (0.138 ml, 0.479 mmol), and potassium acetate (0.076 ml, 1.217 mmol), in 1,4-dioxane (1.84 ml) was degassed with nitrogen for 5 min, treated with dichloro[bis(triphenylphosphoranyl)]palladium (10.4 mg, 0.015 mmol), degassed with nitrogen for another 5 min, and heated at 95 °C for 2 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The filtrate was concentrated to a brown residue. Purification by flash column chromatography using methyl tert-butyl ether in hexanes (0% to 50%) gave the desired product (83.8 mg, 71.4%). LC/MS for $C_{18}H_{27}BO_4Na$ $(M+Na)^+$: m/z = 341.2; Found: 341.2.

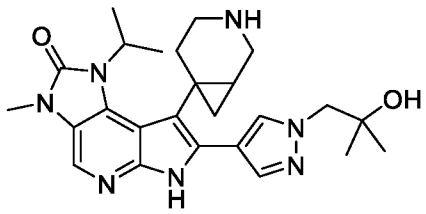
Step 3. 7-(1-(2-Hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



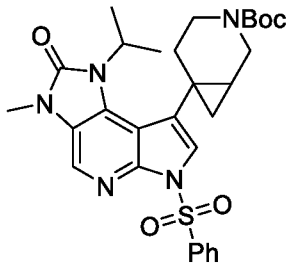
The desired compound was prepared according to the procedure of Example 88, Step 8, using 4,4,5,5-tetramethyl-2-(4-(((tetrahydro-2*H*-pyran-4-yl)oxy)methyl)phenyl)-1,3,2-dioxaborolane in place of thieno[3,2-c]pyridin-2-

ylboronic acid as the starting material. LCMS for $C_{31}H_{39}N_6O_4$ $(M+H)^+$: m/z = 559.3; Found: 559.4.

Example 88. 8-(3-Azabicyclo[4.1.0]heptan-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one



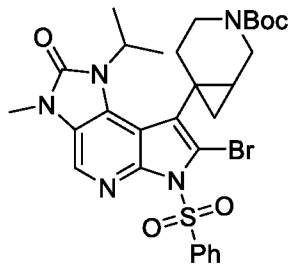
Step 1. tert-Butyl 6-(1-isopropyl-3-methyl-2-oxo-6-(phenylsulfonyl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate



A mixture of 8-bromo-1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (0.150 g, 0.334 mmol), tert-butyl 6-(trifluoro-l4-boraneyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate, potassium salt (0.101 g, 0.334 mmol) [*Org. Lett.* 2017, *19*, 2450-2453], dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.041 g, 0.050 mmol), and cesium carbonate (0.326 g, 1.002 mmol) in toluene (5.06 ml) and water (0.506 ml), was degassed with nitrogen for 5 min, and stirred in a sealed vial at 90 °C for 16 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The organic layer from the filtrate was separated and washed with brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 100%) gave the desired product along with 1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one. This material was repurified by flash column chromatography

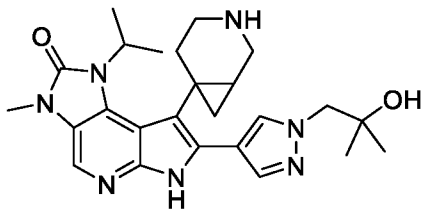
using methanol in dichloromethane (0% to 20%) to give the desired product (151 mg, 79.9%) that still contained 1-isopropyl-3-methyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one in a ratio of ~2:1. LC/MS for $C_{29}H_{36}N_5O_5S$ $(M+H)^+$: m/z = 566.2; Found: 566.3.

Step 2. tert-Butyl 6-(7-bromo-1-isopropyl-3-methyl-2-oxo-6-(phenylsulfonyl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate



The desired compound was prepared according to the procedure of Example 18, Step 7, using tert-butyl 6-(1-isopropyl-3-methyl-2-oxo-6-(phenylsulfonyl)-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate in place of 1-isopropyl-3-methyl-8-phenyl-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one as the starting material. LCMS for $C_{29}H_{35}BrN_5O_5S$ $(M+H)^+$: m/z = 644.2, 646.1; Found: 644.3, 646.2.

Step 3. 8-(3-Azabicyclo[4.1.0]heptan-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



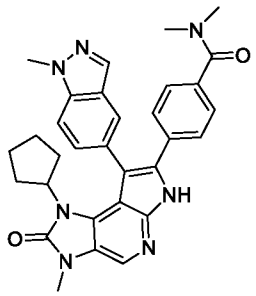
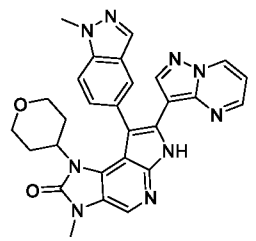
A mixture of tert-butyl 6-(7-bromo-1-isopropyl-3-methyl-2-oxo-6-(phenylsulfonyl)-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.023 g, 0.036 mmol), 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)propan-2-ol (0.024 g, 0.089 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II)

dichloromethane adduct (4.37 mg, 5.35 μmol) in 1,4-dioxane (0.595 ml) and CsF (3M in water) (0.059 ml, 0.178 mmol) was degassed with nitrogen for 5 min, and stirred in sealed vial at 100 °C for 18 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The filtrate was concentrated to a dark oil. This material was diluted with dichloromethane (0.50 mL) and TFA (0.50 mL) and stirred at 20 °C for 30 min. The reaction mixture was concentrated twice from acetonitrile to give the Boc-deprotected intermediate. This material was diluted with methanol (1.3 mL), treated with 3.0 N in water potassium hydroxide (0.714 ml, 2.14 mmol), and stirred at 40 °C for 2 h. The reaction mixture was diluted with trifluoroacetic acid (0.192 ml, 2.50 mmol) followed by methanol and water. This material was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product (3.80 mg, 15.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.45 (br s, 1H), 8.30 (br s, 1H), 8.09 (s, 1H), 8.00 (s, 1H), 7.78 (s, 1H), 5.49 – 5.38 (m, 1H), 4.15 (s, 2H), 3.38 (s, 3H), 3.35 – 3.25 (m, 1H), 3.22 – 3.12 (m, 1H), 3.08 – 3.04 (m, 2H), 2.45 – 2.33 (m, 2H), 1.67 (d, J = 6.6 Hz, 3H), 1.54 (d, J = 6.7 Hz, 3H), 1.26 – 1.21 (m, 1H), 1.18 (s, 3H), 1.14 (s, 3H), 1.11 – 1.01 (m, 2H). LCMS for $C_{25}H_{34}N_7O_2$ $(M+H)^+$: m/z = 464.3; Found: 464.3.

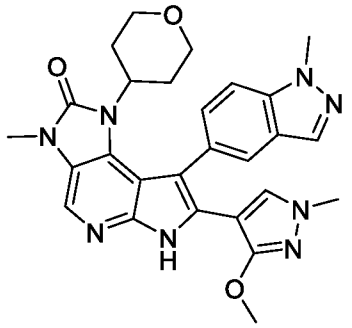
Examples 89-90.

Examples 89-90 in Table 6 were prepared according to the procedures described in Example 18, using appropriately substituted starting materials.

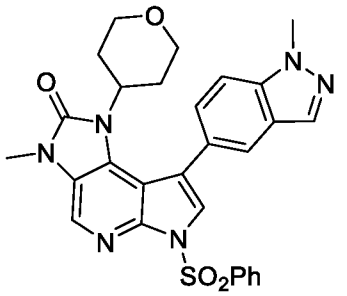
Table 6.

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
89	4-(1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)-*N,N*-dimethylbenzamide		534.3	^1H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.26 (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.46 (dd, J = 8.1 Hz, 0.8 Hz, 1H). 7.44 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 4.11 (s, 3H), 3.38 (s, 3H), 3.35 (m, 2H), 2.92 (s, 3H), 2.84 (s, 3H), 1.97 (m, 1H), 1.83 (m, 1H), 1.41 (m, 1H), 1.28 (m, 1H), 1.22 (m, 1H), 1.04 (m, 1H), 0.60 (m, 1H), 0.09 (m, 1H)
90	3-Methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyrazolo[1,5-a]pyrimidin-3-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		520.2	11.86 (s, 1H), 9.15 (d, J = 6.3 Hz, 1H), 8.75 (m, 1H), 8.31 (s, 1H), 8.12 (s, 1H), 7.96 (s, 1H) 7.89 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.19 (m, 1H), 7.14 (s, 1H), 4.16 (s, 3H), 3.60-3.53 (m, 2H), 3.41 (s, 3H), 3.35 (m, 1H), 2.40 (m, 1H), 2.28 (m, 1H), 1.98 (t, J = 9.8 Hz, 1H), 1.52 (t, J = 9.8 Hz, 1H), 1.24 (d, J = 10.0 Hz, 1H), 1.16 (d, J = 10.0 Hz, 1H).

Example 91. 7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

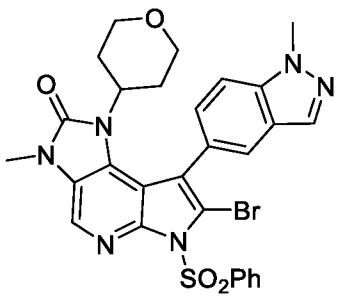


Steps 1-6. 3-Methyl-8-(1-methyl-1H-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



The title compound was prepared according to the procedures described in Example 18, Steps 1 to 6, using appropriately substituted starting materials. LCMS for $C_{28}H_{27}N_6O_4S$ $(M+H)^+$: m/z = 543.2 ; Found: 543.2.

Step 7. 7-Bromo-3-methyl-8-(1-methyl-1H-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



A solution of *3*-methyl-8-(1-methyl-1*H*-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (0.300 g, 0.553 mmol) in dry THF (3 mL) was treated with lithium

diisopropylamide solution (0.7 mL, 1.0 mmol, 2 M in THF/heptane/ethylbenzene; Sigma-Aldrich, 361798) at -78°C in a nitrogen atmosphere. The reaction mixture was stirred at -78°C for 30 minutes before addition of 1,2-dibromotetrachloroethane (0.250 g in 0.5 mL of THF, 0.777 mmol). The reaction mixture was stirred at -78°C for 30 minutes and then quenched by saturated aqueous NH_4Cl (5mL). The resulting mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a yellow amorphous solid. Purification by flash column chromatography using MeOH in dichloromethane (0% to 15%) afforded the desired product as a yellow amorphous solid (0.235 g, 0.379 mmol, 68.5%). LCMS for $C_{28}H_{26}BrN_6O_4S$ $(M+H)^+$: m/z = 621.1, 623.1 ; Found: 621.1, 623.1.

Step 8. 7-(3-Methoxy-1-methyl-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

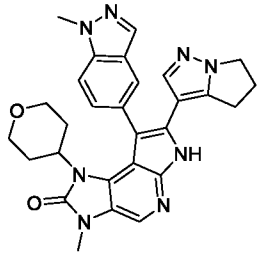
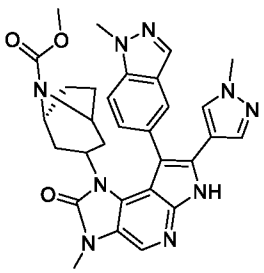
A solution of 7-bromo-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (30.0 mg, 48.3 µmol) and 3-methoxy-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (20.0 mg, 84.0 µmol, Astateh Inc.) in dioxane/water (5:1, 2 mL) was treated with potassium carbonate (20 mg, 144.9 µmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (5 mg, 6.2 µmol) at room temperature followed by stirring at 100°C for 30 minutes. The resulted mixture was added 2 mL of MeOH and sodium hydroxide (0.5 mL, 0.9 mmol, 3 M in water) before it was stired at 60 °C for 1 hour The resulting mixture was diluted with MeOH (2 mL) and acidified with trifluoroacetic acid (TFA, 0.2 mL). The resulting mixture was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% TFA, at flow rate of 60 mL/min) to give the desired product (15.2 mg, 29.6 µmol, 61.2%) as trifluoroacetic acid salt, a white solid. LCMS for $C_{27}H_{29}N_8O_3$ $(M+H)^+$: m/z = 513.2; Found: 513.2. ^1H NMR (500 MHz, DMSO) δ 11.60 (s, 1H), 8.24 (s, 1H), 8.10 (s, 1H), 7.82 (s, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 6.76 (s, 1H), 4.14 (s,

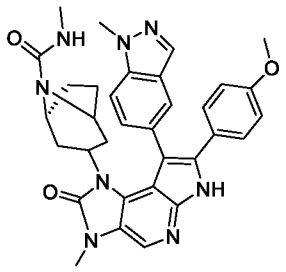
3H), 3.83 (s, 3H), 3.55-3.50 (m, 2H), 3.52 (s, 3H), 3.38 (s, 3H), 3.32 (m, 1H), 2.36 (m, 1H), 2.26 (m, 1H), 1.96 (t, J = 9.8 Hz, 1H), 1.46 (t, J = 9.8 Hz, 1H), 1.18 (d, J = 10.0 Hz, 1H), 1.10 (d, J = 10.0 Hz, 1H).

Examples 92-94.

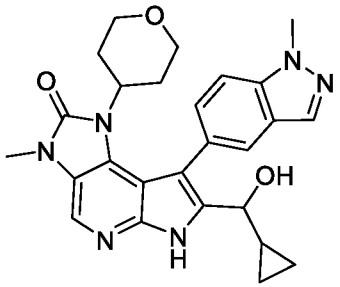
Examples 92-94 in Table 7 were prepared according to the procedures described in Example 91, using appropriately substituted starting materials.

Table 7.

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
92	7-(5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one		509.2	
93	Methyl (1*S*)-3-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate		566.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 8.14-8.09 (m, 2H), 7.87-7.05 (m, 2H), 7.45 (d, J = 9.1 Hz, 1H), 7.39 (s, 1H), 6.73 (s, 1H), 4.13 (s, 3H), 3.73 (s, 3H), 3.63-3.60 (m, 3H), 3.56 (s, 3H), 3.37 (s, 3H), 1.32 – 1.19 (m, 6H), 0.15 (t, J = 8.9 Hz, 1H), 0.00 (t, J = 8.9 Hz, 1H).

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
94	(1*S*)-3-(7-(4-Methoxyphenyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)-*N*-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide		591.3	

Example 95. 7-(Cyclopropyl(hydroxy)methyl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one



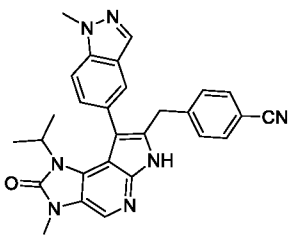
A solution of 3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (0.200 g, 0.369 mmol, Example 91, Step 6,) in dry THF (3 mL) was treated with lithium diisopropylamide solution (0.5 mL, 1.0 mmol, 2 M in THF/heptane/ethylbenzene; Sigma-Aldrich, 361798) at -78°C in a nitrogen atmosphere. The reaction mixture was stirred at -78°C for 30 minutes before addition of cyclopropanecarbaldehyde (105.0 mg, 1.5 mmol). The reaction mixture was stirred at -78°C for 30 minutes and then quenched by saturated aqueous NH_4Cl (5 mL). The resulting mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a yellow mixture. A solution of the resulted mixture in MeOH (4 mL) was treated with sodium hydroxide (0.6 mL, 0.9 mmol, 3 M in water), and the reaction mixture was stirred at 60 °C for 1 hour. The

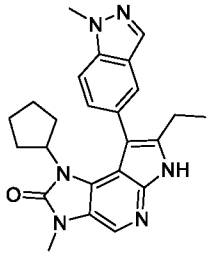
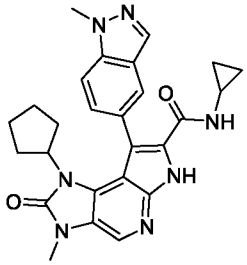
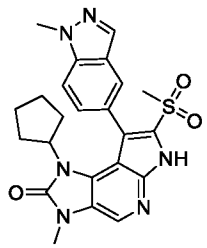
resulting mixture was diluted with MeOH (5 mL) and acidified with trifluoroacetic acid (TFA, 0.4 mL). The resulting mixture was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% TFA, at flow rate of 60 mL/min) to give the desired product (37.5 mg, 0.079 mmol, 21.5%) as trifluoroacetic acid salt, a white solid. LCMS for $C_{26}H_{28}N_6O_3$ $(M+H)^+$: m/z = 473.2; Found: 473.2. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.46 (s, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 16.2 Hz, 1H), 6.99 (d, *J* = 9.3 Hz, 1H), 6.73 (dd, J = 16.2 Hz, 9.3 Hz, 1H), 3.38 (s, 3H), 3.03 (m, 1H), 2.87 (m, 1H), 2.83 (m, 2H), 2.68 (s, 3H), 2.62 (m, 1H), 1.84 -1.53 (m, 2H), 1.36 (m, 1H), 0.86 (m, 1H), 0.59-0.35 (m, 3H), -0.21 (m, 1H), -0.39 (m, 1H), -0.43 (m, 1H).

Examples 96-99.

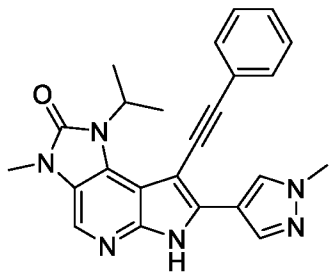
Examples 96-99 in Table 8 were prepared according to the procedures described in Example 95, using appropriately substituted starting materials. For example, instead of using cyclopropanecarbaldehyde for functionalizing the R^4 position of Example 95 (see *e.g. S*tep 7), 4-(bromomethyl)benzonitrile, ethyl iodide, cyclopropylcarbamic chloride and methanesulfonyl chloride were used to afford the compounds of Examples 96, 97, 98 and 99, respectively.

Table 8.

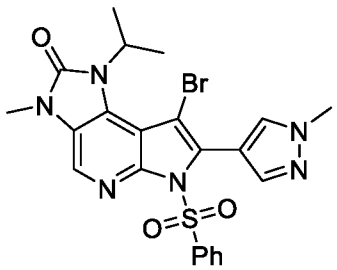
Ex. No.	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR
96	4-((1-Isopropyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)methyl)benzonitrile		476.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.72 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 0.5 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 2H), 4.10 (s, 3H), 3.97 (d, J = 7.8 Hz, 2H), 3.55 (m, 1H), 3.35 (s, 3H), 0.97 (d, *J* = 7.4 Hz, 3H), 0.82 (d, *J* = 7.4 Hz, 3H)

Ex. No.	Name	Structure	LCMS $[M+H]^+$	^1H NMR
97	1-Cyclopentyl-7-ethyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		415.2	
98	1-Cyclopentyl-N-cyclopropyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxamide		470.2	
99	1-Cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(methylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one		465.2	

Example 100. 1-Isopropyl-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-8-(phenylethynyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-b]pyridin-2(1*H*)-one



Step 1. 8-Bromo-1-isopropyl-3-methyl-7-(1-methyl-1H-pyrazol-4-yl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

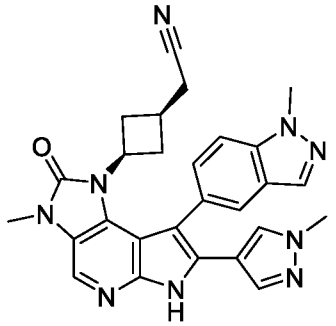


The title compound was prepared according to the procedures described in Example 75, Step 7, using appropriately substituted starting materials. LC/MS for $C_{22}H_{22}BrN_6O_3S$ $(M+H)^+$: m/z = 528.1, 530.1; Found: 528.1, 530.1.

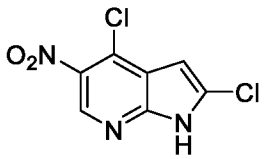
Step 2. 1-isopropyl-3-methyl-7-(1-methyl-1H-pyrazol-4-yl)-8-(phenylethynyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

A mixture of 8-bromo-1-isopropyl-3-methyl-7-(1-methyl-1H-pyrazol-4-yl)-6-(phenylsulfonyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one (0.008 g, 0.015 mmol), 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (8.62 mg, 0.038 mmol), and tetrakis(triphenylphosphine)palladium(0) (2.62 mg, 2.27 μmol) in 1,4-dioxane (0.252 mL) and 1.0 N sodium carbonate in water (0.045 mL, 0.045 mmol) was degassed with nitrogen for 5 min, and stirred in a sealed vial at 90 °C for 16 h. The reaction mixture was diluted with ethyl acetate, passed through a 0.45 micron filter, and rinsed with ethyl acetate. The filtrate was concentrated to a yellow oil and placed under vacuum at reduced pressure for 30 min. This material was dissolved in methanol (1.00 mL), treated with 3.0 N potassium hydroxide in water (0.302 mL, 0.907 mmol), and stirred at 40 °C for 1 h. The reaction mixture was diluted with trifluoroacetic acid (0.093 mL, 1.21 mmol), followed by acetonitrile, methanol, and water. This material was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product (2.0 mg, 25.2%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.42 (s, 1H), 8.26 (s, 1H), 8.14 (s, 1H), 7.55 (d, J = 7.4 Hz, 2H), 7.50 (dd, J = 7.4, 7.4 Hz, 2H), 7.43 (dd, 7.4, 7.4 Hz, 1H), 5.93 (hept, J = 6.8 Hz, 1H), 3.97 (s, 3H), 3.40 (s, 3H), 1.60 (d, J = 6.8 Hz, 6H). LCMS for $C_{24}H_{22}N_6O$ $(M+H)^+$: m/z = 411.2; Found: 411.2.

Example 101. 2-((1*S*,3*S*)-3-(3-Methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)acetonitrile

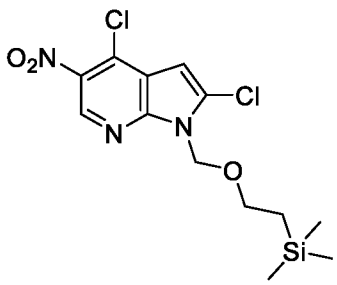


Step 1. 2,4-Dichloro-5-nitro-1H-pyrrolo[2,3-b]pyridine



To a round bottom flask containing 4-chloro-5-nitro-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (PharmaBlock, 5.09 g, 23.83 mmol) was added $POCl_3$ (100.0 ml). The mixture was heated to 100 °C for 3 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. To the residue was added THF (150 mL), water (150 mL), followed by sat. $NaHCO_3$ (aq, 150 ml). The mixture was stirred at room temperature for 30 min, and then concentrated *in vacuo* to remove most of THF. The resulting suspension was filtered. The filter cake was rinsed with water, and dried *in vacuo* to give the desired product as a beige solid (5.26 g, 95%). LCMS calculated for $C_7H_4Cl_2N_3O_2$ $(M+H)^+$ m/z = 232.0; found 232.0.

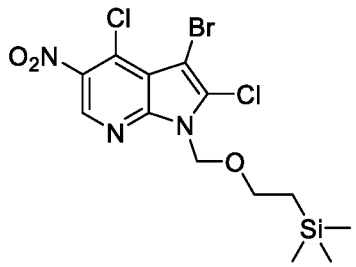
Step 2. 2,4-Dichloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine



To a solution of 2,4-dichloro-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (5.26 g, 22.67

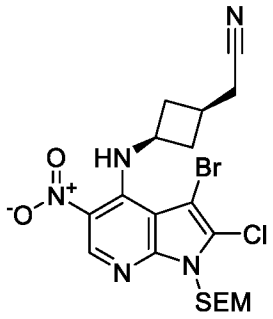
mmol) in DMF (150.0 ml) at 0 °C was added sodium hydride (1.423 g, 35.6 mmol). The mixture was stirred at 0 °C for 30 min, and then was allowed to warm to room temperature. After stirring at room temperature for 1 h, the reaction mixture was cooled to 0 °C. A solution of (2-(chloromethoxy)ethyl)trimethylsilane (5.923 g, 35.5 mmol) in DMF (20.0 mL) was added slowly. The mixture was stirred at 0 °C for 30 min, and then was allowed to warm to room temperature and stirred for another 1 h. The reaction was quenched with sat. NH_4Cl (aq), and extracted with EtOAc. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (240 g, 0-50% EtOAc in DCM) to give the desired product as a pale yellow solid (6.02 g, 73%). LCMS calculated for $C_{13}H_{18}Cl_2N_3O_3Si$ (M+H)+ m/z = 362.0; found 362.1.

Step 3. 3-Bromo-2,4-dichloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine



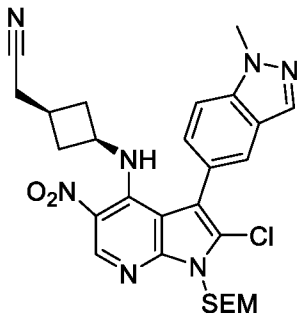
To a solution of dichloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1742.2 mg, 4.81 mmol) in DCM (12.0 ml) and DMF (12.00 ml) was added 1-bromopyrrolidine-2,5-dione (1043 mg, 5.86 mmol). The mixture was stirred at room temperature for 16 h. The reaction was then diluted with DCM, washed with 2 M K_2CO_3 (aq). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (40 g, 0-50% EtOAc in DCM) to give the desired product as a yellow solid (2.01 g, 95%). LCMS calculated for $C_{13}H_{17}BrCl_2N_3O_3Si$ $(M+H)^+$ m/z = 440.0, 442.0; found 440.0, 442.0.

Step 4. 2-((1S,3S)-3-((3-Bromo-2-chloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)cyclobutyl)acetonitrile



To a solution of 3-bromo-2,4-dichloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (701.3 mg, 1.590 mmol) in 2-propanol (60.0 ml) was added 2-((1s,3s)-3-aminocyclobutyl)acetonitrile, HCl salt (257.8 mg, 1.758 mmol) followed by DIPEA (3.00 mL, 17.18 mmol). The mixture was stirred at 100 °C for 90 min. After cooling to room temperature, the reaction was concentrated *in vacuo*. The resulting residue was purified on silica gel (40g, 0-100% EtOAc in DCM) to give the desired product as a yellow solid (783.1 mg, 96%). LCMS calculated for $C_{19}H_{26}BrClN_5O_3Si$ (M+H)+ m/z = 514.1, 516.1; found 514.1, 516.1.

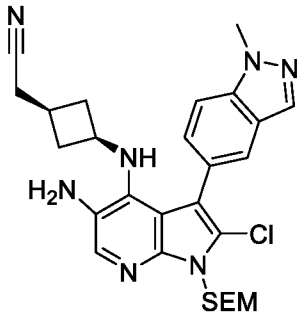
Step 5. 2-((1S,3S)-3-((2-Chloro-3-(1-methyl-1H-indazol-5-yl)-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)cyclobutyl)acetonitrile



To a screw-cap vial equipped with a magnetic stir bar was added 2-((1*S*,3*S*)-3-((3-bromo-2-chloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)amino)cyclobutyl)acetonitrile (783.1 mg, 1.521 mmol), (1-methyl-1*H*-indazol-5-yl)boronic acid (301.4 mg, 1.713 mmol), tetrakis(triphenylphosphine)palladium(0) (464.7 mg, 0.402 mmol) and cesium

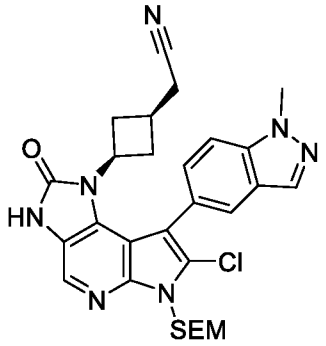
carbonate (1865 mg, 5.72 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (20.0 ml) was added, followed by water (3.0 mL). The reaction was heated at 100 °C for 90 min. After cooling to room temperature, the reaction mixture was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in DCM) to give the desired product as an orange foamy solid. (740.2 mg, 86%). LCMS calculated for $C_{27}H_{33}ClN_7O_3Si$ (M+H)+ m/z = 566.2; found 566.3.

Step 6. 2-((1S,3S)-3-((5-Amino-2-chloro-3-(1-methyl-1H-indazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)cyclobutyl)acetonitrile



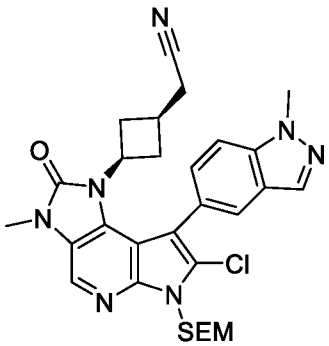
To a mixture of 2-((1*S*,3*S*)-3-((2-chloro-3-(1-methyl-1*H*-indazol-5-yl)-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)amino)cyclobutyl)acetonitrile (740.2 mg, 1.307 mmol) and iron powder (1095.7 mg, 19.62 mmol) was added THF (30.0 ml) and ethanol (10.00 ml). Then 1.0 N HCl (aq)) (7.0 mL, 7.00 mmol) was added. The mixture was stirred at 65 °C for 4 hour. After cooling to room temperature, the reaction mixture was filtered. The filter cake was rinsed with DCM. The filtrate was washed with 2 M K_2CO_3 (aq). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in DCM) to give the desired product as a yellow foamy solid (457.1 mg, 65%). LCMS calculated for $C_{27}H_{35}ClN_7OSi$ (M+H)+ m/z = 536.2; found 536.2.

Step 7. 2-((1s,3s)-3-(7-Chloro-8-(1-methyl-1H-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)acetonitrile



To a solution of 2-((1*S*,3*S*)-3-((5-amino-2-chloro-3-(1-methyl-1*H*-indazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)amino)cyclobutyl)acetonitrile (457.1 mg, 0.853 mmol) in THF (10.0 ml) was added CDI (561.3 mg, 3.46 mmol), followed by pyridine (10.0 mL) and DIPEA (3.0 mL). The mixture was stirred at 90 °C for 5 h. After cooling to room temperature, the reaction was concentrated. The residue was purified on silica gel (40g, 0-100% EtOAc in DCM) to give the desired product as a white solid (414.9 mg, 87%). LCMS calculated for $C_{28}H_{33}ClN_7O_2Si$ (M+H)+ m/z = 562.2; found 562.2.

Step 8. 2-((1S,3S)-3-(7-Chloro-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)acetonitrile



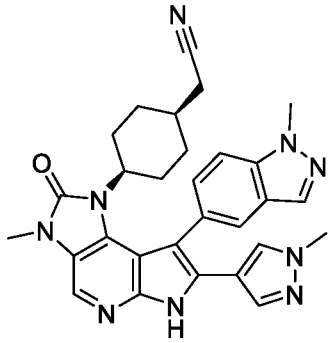
To a solution of 2-((1*S*,3*S*)-3-(7-chloro-8-(1-methyl-1H-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)acetonitrile (414.9 mg, 0.738 mmol) in DMF (12.0 ml) was added Cs_2CO_3 (1583 mg, 4.86 mmol) followed by MeI (2.0 M in MTBE) (600.0 µL,

1.200 mmol). The mixture was stirred at room temperature for 40 min. The reaction was then filtered and concentrated. The residue was purified on silica gel (40g, 0-100% EtOAc in DCM) to give the desired product as an off-white solid (409.5 mg, 96%). LCMS calculated for $C_{29}H_{35}ClN_7O_2Si$ (M+H)+ m/z = 576.2; found 576.3.

Step 9: 2-((1S,3S)-3-(3-Methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)acetonitrile

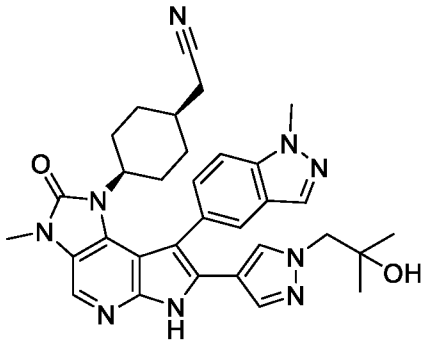
To a screw-cap vial equipped with a magnetic stir bar was added 2-((1*S*,3*S*)-3-(7-chloro-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)acetonitrile (16.3 mg, 0.028 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (13.4 mg, 0.064 mmol),dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine - (2'-aminobiphenyl-2-yl)(chloro)palladium (1:1) (3.2 mg, 4.07 μmol) and cesium carbonate (47.3 mg, 0.145 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (3.0 ml) was added, followed by degassed water (300.0 μL). The reaction was heated at 60 °C for 16 h. After cooling to room temperature, the reaction was concentrated. The residue was dissolved in DCM (5.0 mL) and treated with TFA (5.0 mL). After stirring at room temperature for 2 h, the reaction was concentrated. The residue was dissolved in MeOH (3.0 mL) and treated with ethylenediamine (500.0 μL, 7.40 mmol). After stirring at room temperature for 1 h, the mixture was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product as its TFA salt. LCMS calculated for $C_{27}H_{26}N_9O$ $(M+H)^+$: m/z = 492.2; found: 492.2. ^1H NMR (600 MHz, DMF-d_7) δ 12.67 (br, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 7.99 (overlap, 2H), 7.66 (s, 1H), 7.58 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.38 (s, 1H), 4.25 (s, 3H), 3.82 (s, 3H), 3.65 (m, 1H), 3.47 (s, 3H), 2.66 (m, 1H), 2.55 (m, 1H), 2.51 (d, *J* = 7.4 Hz, 2H), 1.85 (m, 1H), 1.59 (m, 1H), 0.94 (m, 1H).

Example 102. 2-((1*S*,4*S*)-4-(3-Methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile



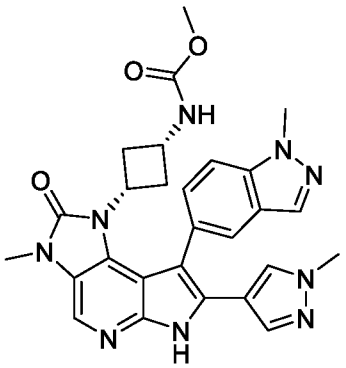
The title compound was prepared according to the procedures described in Example 101, using appropriately substituted starting materials. LCMS calculated for $C_{29}H_{30}N_9O$ $(M+H)^+$: m/z = 520.3; found: 520.2.

Example 103. 2-((1*S*,4*S*)-4-(7-(1-(2-Hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile

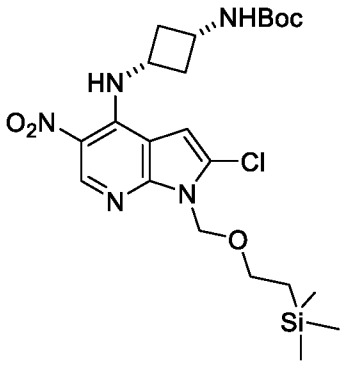


The title compound was prepared according to the procedures described in Example 101, using appropriately substituted starting materials. LCMS calculated for $C_{32}H_{36}N_9O_2$ $(M+H)^+$: m/z = 578.3; found: 578.3.

Example 104. Methyl ((1*S*,3*S*)-3-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate

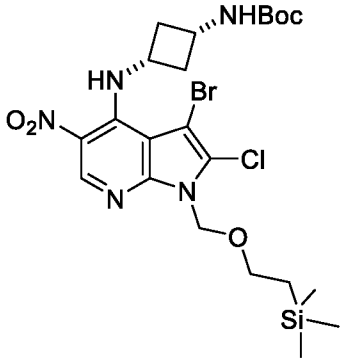


Step 1. tert-Butyl ((1S,3S)-3-((2-chloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)cyclobutyl)carbamate



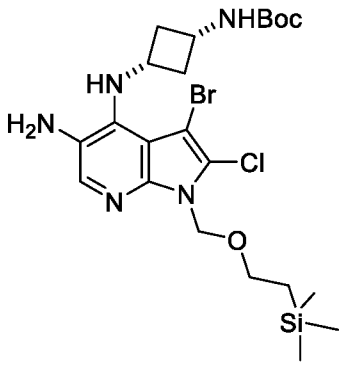
In a flask 2,4-dichloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.17g, 5.99 mmol, Example 101, Step 2) was diluted with THF (29.9 ml). To this was sequentially added tert-butyl ((1*S*,3*S*)-3-aminocyclobutyl)carbamate (1.673 g, 8.98 mmol) and triethylamine (2.505 ml, 17.97 mmol). After 15 minutes complete consumption of the starting material was observed by LCMS. The crude reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford the desired product (3.18g, 6.21 mmol) LC-MS calculated for $C_{22}H_{35}ClN_5O_5Si$ $(M+H)^+$: m/z = 512.2; found 512.3.

Step 2. tert-Butyl ((1S,3S)-3-((3-bromo-2-chloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)cyclobutyl)carbamate



To a solution of tert-butyl ((1*S*,3*S*)-3-((2-chloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)amino)cyclobutyl)carbamate (3.18g, 6.21 mmol) in DCM (62.1 ml) was added NBS (1.326 g, 7.45 mmol). The reaction was complete within 5 minutes. The crude reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford the desired product as an impure mixture. Taken on as-is. LC-MS calculated for $C_{22}H_{34}BrClN_5O_5Si$ $(M+H)^+$: m/z = 590.1, 592.1; found 590.1, 592.1.

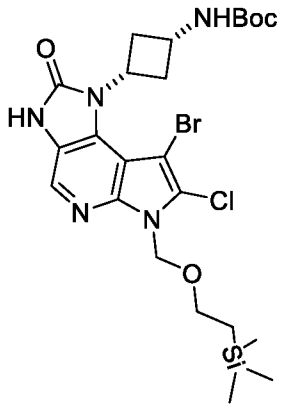
Step 3. tert-Butyl ((1S,3S)-3-((5-amino-3-bromo-2-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)cyclobutyl)carbamate



In a flask, *tert*-butyl ((1*S*,3*S*)-3-((3-bromo-2-chloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-*b*]pyridin-4-yl)amino)cyclobutyl)carbamate was diluted with a mixture of THF/water/MeOH (12 mL/6 mL/12 mL). To this was then sequentially added ammonium chloride (1.03 g,

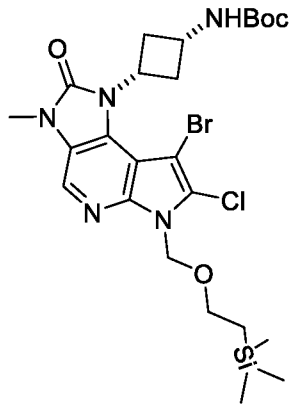
19.2 mmol) and iron (765 mg, 13.7 mmol). The reaction mixture was heated to reflux for one hour after which time it was cooled to room temperature and filtered over celite to remove the iron. The resulting filtrate was then extracted with 5% MeOH in DCM (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude residue was taken on as-is without further purification. LC-MS calculated for $C_{22}H_{36}BrClN_5O_3Si$ $(M+H)^+$: m/z = 560.1, 562.1; found 560.0, 562.1.

Step 4. tert-Butyl ((1S,3S)-3-(8-bromo-7-chloro-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)carbamate



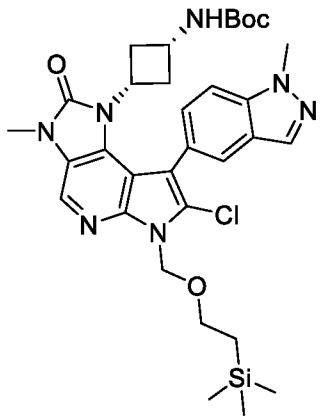
The crude intermediate of Step 3 was diluted with DCM (14 mL). To this was then added CDI (888 mg, 5.48 mmol) and was heated to reflux overnight. The crude reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford the desired product (1.07 g, 1.82 mmol). LC-MS calculated for $C_{23}H_{34}BrClN_5O_4Si$ $(M+H)^+$: m/z = 586.1, 588.1; found 586.0, 588.1.

Step 5. tert-Butyl ((1S,3S)-3-(8-bromo-7-chloro-3-methyl-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)carbamate



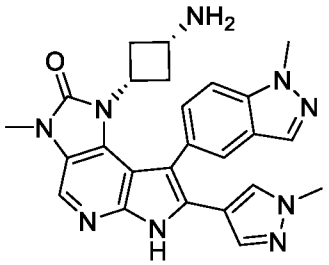
In a flask *tert*-butyl ((1*S*, 3*S*)-3-(8-bromo-7-chloro-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate was combined with cesium carbonate (2.68 g, 8.22 mmol), diluted with THF (14 mL), to this was then added iodomethane (171 µL, 2.74 mmol) and was allowed to stir overnight. The crude reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford the desired product (491 mg, 0.817 mmol). LC-MS calculated for $C_{24}H_{36}BrClN_5O_4Si$ $(M+H)^+$: m/z = 600.1, 602.1; found 600.1, 602.1.

Step 6. tert-Butyl ((1S,3S)-3-(7-chloro-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)carbamate



In a vial *tert*-butyl ((1*S*,3*S*)-3-(8-bromo-7-chloro-3-methyl-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate (150 mg, 0.25 mmol) was combined with cesium carbonate (285 mg, 0.874 mmol), and tetrakis(triphenylphosphine)palladium(0) (87 mg, 0.075 mmol), and (1-methyl-1H-indazol-5-yl)boronic acid (43.9 mg, 0.250 mmol). The vial is placed under vacuum and backfilled with nitrogen 3 times. To this was then added dioxane (4.99 ml) and water (450 µL, 24.96 mmol). The resulting mixture was heated to 100 °C for 90 minutes. The crude reaction mixture cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford the desired product as an impure mixture (242 mg, 0.371 mmol). Taken on without additional purification. LC-MS calculated for $C_{32}H_{43}ClN_7O_4Si$ $(M+H)^+$: m/z = 652.3; found 652.5.

Step 7. 1-((1S,3S)-3-Aminocyclobutyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



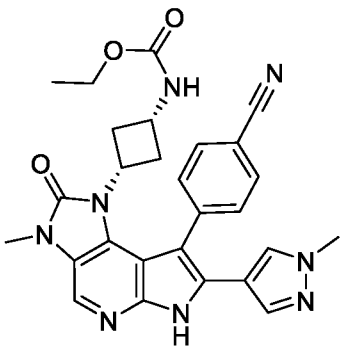
In a vial, tert-butyl ((1*S*,3*S*)-3-(7-chloro-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2H)-yl)cyclobutyl)carbamate (255 mg, 0.391 mmol) was combined with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (244 mg, 1.173 mmol), XPhos Pd G2 (61.5 mg, 0.078 mmol), cesium carbonate (510 mg, 1.564 mmol), and a 4:1 mixture of Dioxane water (3.2 mL/0.80 mL). The solvent was sparged with nitrogen and heated to 70 °C for 30 minutes. The crude reaction mixture cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford the desired product as an impure mixture which was taken on without further purification. The purified residue was treated with a 1:1 mixture of TFA (2 mL) and

DCM (2 mL) and was stirred at RT until deprotection of the Boc group was observed after which time the crude reaction mixture was concentrated under reduced pressure. The crude residue was then taken up in a 2:2:1 mixture of MeOH:THF:2M NaOH totaling 5 mL. Reaction was heated at 40 °C until the amino alcohol of the SEM protecting group was completely removed. The crude reaction mixture was acidified with saturate ammonium chloride and extracted with a 3:1 chloroform IPA mixture. The organic layers were reserved and concentrated under reduced pressure. A yield was not obtained for this transformation and was taken on without further purification. LC-MS calculated for $C_{32}H_{43}ClN_7O_4Si$ $(M+H)^+$: m/z = 468.2; found 468.3.

Step 8. Methyl ((1S,3S)-3-(3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)carbamate

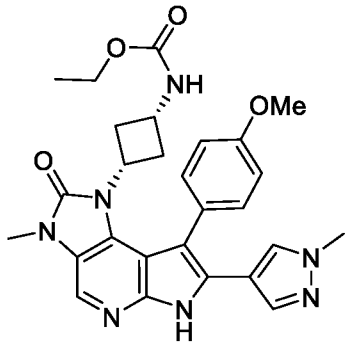
A portion of the crude residue from the above transformation (75 mg, 0.151 mmol) was diluted with DCM (3 mL). To this was sequentially added trimethylamine (0.1 mL, 0.754 mmol) and methyl chloroformate (0.018 mL, 0.226 mmol) and was stirred at room temperature until the reaction was complete. The crude reaction mixture was purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LC-MS calculated for $C_{27}H_{28}N_9O_3$ $(M+H)^+$: m/z = 526.2; found 526.2.

Example 105. Ethyl ((1*S*,3*S*)-3-(8-(4-cyanophenyl)-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate



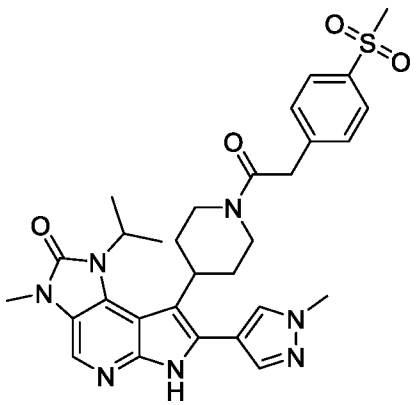
The title compound was prepared according to the procedures described in Example 104, using (4-cyanophenyl) boronic acid instead of (1-methyl-1H-indazol-5-yl)boronic acid in Step 6 and ethyl chloroformate instead of methyl chloroformate in Step 8. LC-MS calculated for $C_{27}H_{27}N_8O_3$ $(M+H)^+$: m/z = 511.2; found 511.2.

Example 106. Ethyl ((1*S*,3*S*)-3-(8-(4-methoxyphenyl)-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate

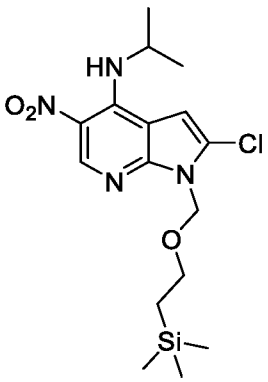


The title compound was prepared according to the procedures described in Example 104, using 4-methoxyphenyl boronic acid instead of (1-methyl-1H-indazol-5-yl) boronic acid in Step 6, and ethyl chloroformate instead of methyl chloroformate in Step 8. LC-MS calculated for $C_{27}H_{30}N_7O_4$ $(M+H)^+$: m/z = 516.2; found 516.2.

Example 107. 1-Isopropyl-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-8-(1-(2-(4-(methylsulfonyl)phenyl)acetyl)piperidin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one

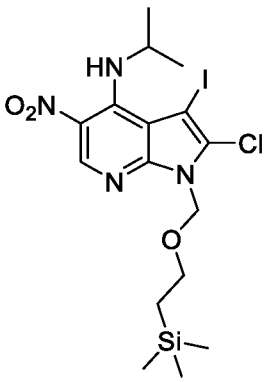


Step 1. 2-Chloro-N-isopropyl-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-amine



The title compound was prepared according to the procedure of Example 75, Step 2, using 2,4-dichloro-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine in place of 2-bromo-4-chloro-5-nitro-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine as the starting material. LCMS for $C_{16}H_{26}ClN_4O_3Si$ $(M+H)^+$: m/z = 385.1; Found: 385.2.

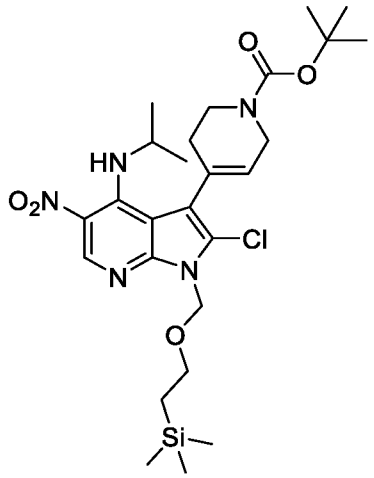
Step 2. 2-Chloro-3-iodo-N-isopropyl-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-amine



A solution of 2-chloro-*N*-isopropyl-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (0.200 g, 0.520 mmol) in DMF (2.08 ml) was treated with NIS (0.292 g, 1.30 mmol). The reaction mixture was stirred at 70 °C for 16 hrs, then added into 20% sodium thiosulfate solution. The product was extracted from the aqueous layer with ethyl acetate (3x). The combined organic layers were washed with brine (2x), then dried over magnesium sulfate, filtered, and concentrated to a yellow oil. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 30%) gave the desired

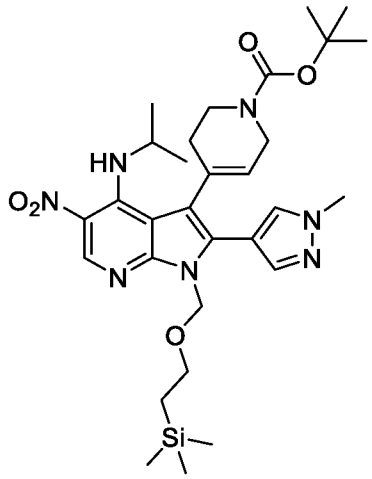
product (251 mg, 94.7%) as a yellow oil. LC/MS for $C_{16}H_{25}ClIN_4O_3Si$ $(M+H)^+$: m/z = 510.0; Found: 511.1.

Step 3. tert-Butyl 4-(2-chloro-4-(isopropylamino)-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate



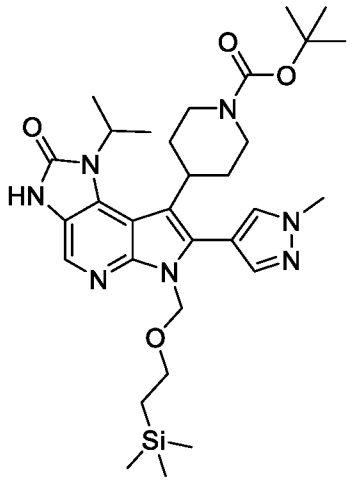
A solution of 2-chloro-3-iodo-*N*-isopropyl-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine (0.125 g, 0.245 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate [Combi-Blocks, catalog #: PN-8629] (0.098 g, 0.318 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.030 g, 0.037 mmol) in *p*-dioxane (3.06 ml) and 1.0 M potassium carbonate in water (0.734 ml, 0.734 mmol) was bubbled with nitrogen for 5 minutes, then stirred in a sealed vial at 70 °C for 4 hrs. Ethyl acetate was added to the reaction mixture and it was filtered through a 0.45 micron cartridge. Residual reaction mixture was rinsed through the cartridge with ethyl acetate. The filtrate was concentrated to a yellow oil. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 100%) gave the desired product (109 mg, 78.4%) as a yellow solid. LC/MS for $C_{26}H_{41}ClN_5O_5Si$ $(M+H)^+$: m/z = 566.3; Found: 566.3.

Step 4. tert-Butyl 4-(4-(isopropylamino)-2-(1-methyl-1H-pyrazol-4-yl)-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate



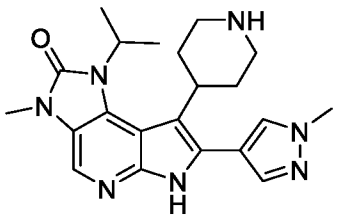
A solution of *tert*-butyl 4-(2-chloro-4-(isopropylamino)-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (0.126 g, 0.223 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.093 g, 0.445 mmol) in *p*-dioxane (3.56 ml) and water (0.890 ml) was treated with cesium carbonate (0.218 g, 0.668 mmol) and degassed with nitrogen for 5 mins. The reaction mixture was treated with XPhos Pd G2 (0.053 g, 0.067 mmol), degassed with nitrogen for another 5 mins, and stirred at 70 °C for 2 hrs. Ethyl acetate was added to the reaction mixture and it was filtered through a 0.45 micron cartridge. Residual reaction mixture was rinsed through the cartridge with ethyl acetate. The filtrate was concentrated to a dark oil. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 100%) gave the desired product (89 mg, 65.4%) as a yellow oil. LC/MS for $C_{30}H_{46}N_7O_5Si$ $(M+H)^+$: m/z = 612.3; Found: 612.3.

Step 5. tert-Butyl 4-(1-isopropyl-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)piperidine-1-carboxylate



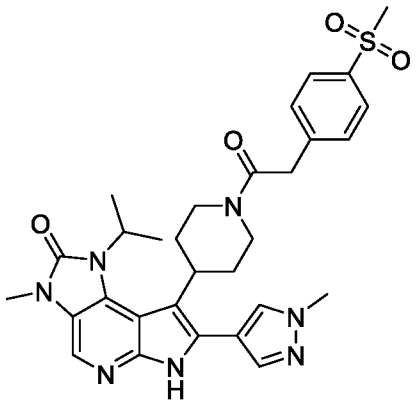
A mixture of *tert*-butyl 4-(4-(isopropylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (0.041 g, 0.067 mmol) and 10% Pd-C (0.029 g, 0.027 mmol) in ethyl acetate (3.35 ml) and triethylamine (0.019 ml, 0.134 mmol) was put through three evacuation-backfill cycles with nitrogen, followed by three with hydrogen. The mixture was heated in a sealed vial at 65 °C for 41 hrs. After cooling to room temperature, the reaction mixture was passed through a 0.45 micron syringe filter. Residual reaction mixture was rinsed through the syringe filter with ethyl acetate. The filtrate was concentrated to a white foam and placed on high vacuum for 3 hrs, giving 47 mg of intermediate that was carried forward without further purification. The residue was dissolved in DMF (0.84 mL) and treated with CDI (0.054 g, 0.335 mmol). The solution was stirred in a sealed vial at 60 °C for 10 hrs, then cooled to room temp. The reaction mixture was added into DI water and the product extracted with ethyl acetate (3x). The combined organic layers were washed with brine (2x), then dried over magnesium sulfate, filtered, and concentrated to a red oil. Purification by flash column chromatography using ethyl acetate [w/ 10% MeOH] in hexanes (0% to 100%) gave the desired product (19 mg, 46.5%) as a pink foam. LC/MS for $C_{31}H_{48}N_7O_4Si$ $(M+H)^+$: m/z = 610.4; Found: 610.5.

Step 6. 1-Isopropyl-3-methyl-7-(1-methyl-1H-pyrazol-4-yl)-8-(piperidin-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



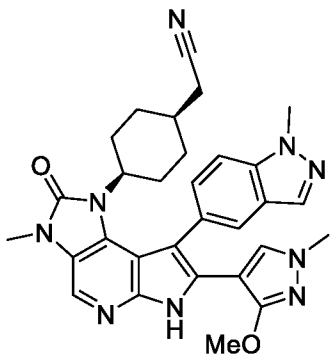
A solution of *tert*-butyl 4-(1-isopropyl-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)piperidine-1-carboxylate (0.019 g, 0.031 mmol) in THF (0.519 ml) was treated with cesium carbonate (0.030 g, 0.093 mmol). After 5 mins, iodomethane (0.014 ml, 0.218 mmol) was added, giving solids. The reaction mixture was stirred in a sealed vial for 16 hrs. The reaction mixture was passed through a 0.45 micron syringe filter. Residual reaction mixture was rinsed through the syringe filter with THF (2 x 0.5 mL). The filtrate was concentrated to a red oil and placed on high vacuum for 30 mins. The residue was dissolved in a mixture of dichloromethane (0.50 mL) and TFA (0.50 mL). Stirred at room temp for 2 hrs. The reaction mixture was concentrated twice from acetonitrile, then placed on high vacuum for 1 hr. The residue was dissolved in a mixture of THF (0.47 mL) and methanol (0.47 mL). To this was added 1.0 N sodium hydroxide in water (0.467 ml, 0.467 mmol) and the reaction stirred for 16 hrs at room temp. Trifluoroacetic acid (0.060 ml, 0.779 mmol) was added to the reaction mixture, followed by methanol. This material was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product (11.6 mg, 59.9%) as a white solid. ^{1}H NMR (600 MHz, DMSO) δ 11.83 (s, 1H), 8.49 (m, 2H), 8.13 (s, 1H), 8.01 (s, 1H), 7.73 (s, 1H), 4.55 (hept, J = 6.8 Hz, 1H), 3.95 (s, 3H), 3.39 (m, 5H), 3.13 (tt, J = 12.5, 3.3 Hz, 1H), 2.83 (qd, J = 12.1, 6.3 Hz, 2H), 2.11 – 2.01 (m, 2H), 1.90 (d, J = 14.0 Hz, 2H), 1.64 (d, J = 6.7 Hz, 6H). LCMS for $C_{21}H_{28}N_7O$ $(M+H)^+$: m/z = 394.2; Found: 394.2.

Step 7. 1-Isopropyl-3-methyl-7-(1-methyl-1H-pyrazol-4-yl)-8-(1-(2-(4-(methylsulfonyl)phenyl)acetyl)piperidin-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

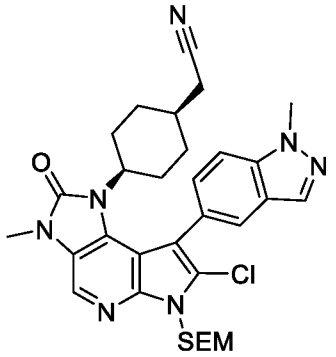


A solution of 1-isopropyl-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-8-(piperidin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one, 2TFA (0.0014 g, 2.252 µmol) and 2-(4-(methylsulfonyl)phenyl)acetic acid (0.965 mg, 4.50 µmol) in DMF (0.150 ml) was treated with HATU (1.285 mg, 3.38 µmol). After a few minutes, triethylamine (6.28 µL, 0.045 mmol) was added. The solution was stirred at room temp for 30 mins. At this point, methanol and DI water were added. This material was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product (1.3 mg,82.0%) as a white solid. LCMS for $C_{30}H_{36}N_7O_4S$ $(M+H)^+$: m/z = 590.3; Found: 590.3.

Example 108. 2-((1*S*,4*S*)-4-(7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile



Step 1-8. 2-((1S,4S)-4-(7-chloro-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclohexyl)acetonitrile



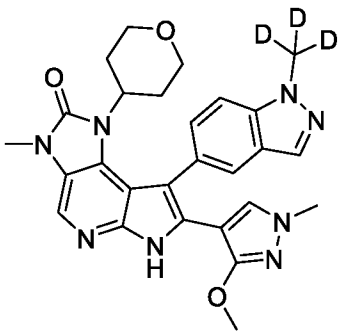
The title compound was prepared according to the procedures described in Example 101 using appropriately substituted starting materials. LCMS calculated for $C_{31}H_{39}ClN_7O_2Si$ $(M+H)^+$: m/z = 604.3; found: 604.2.

Step 9. 2-((1S,4S)-4-(7-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclohexyl)acetonitrile

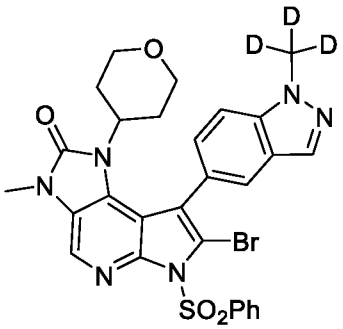
To a screw-cap vial equipped with a magnetic stir bar was added 2-((1*S*,4*S*)-4-(7-chloro-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile (18.0 mg, 0.030 mmol), 3-methoxy-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (20.0 mg, 0.084 µmol, Astateh Inc.) ,dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine - (2'-aminobiphenyl-2-yl)(chloro)palladium (1:1) (3.0 mg, 3.82 µmol) and cesium carbonate (45.0 mg, 0.138 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (3.0 ml) was added, followed by degassed water (300.0 µL). The reaction was heated at 60 °C for 16 h. After cooling to room temperature, the reaction was concentrated. The residue was dissolved in DCM (5.0 mL) and treated with TFA (5.0 mL). After stirring at room temperature for 2 h, the reaction was concentrated. The residue was dissolved in MeOH (3.0 mL) and treated with ethylenediamine (500.0 µL, 7.40 mmol). After stirring at room temperature for 1 h, the mixture was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of

acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product as its TFA salt. LCMS calculated for $C_{30}H_{32}N_9O_2$ $(M+H)^+$: m/z = 550.3; found: 550.3. ^{1}H NMR (600 MHz, DMF-d_7) δ 12.09 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 8.6, Hz, 1H), 6.73 (s, 1H), 4.24 (s, 3H), 4.00 (s, 3H), 3.57 (s, 3H), 3.50 (s, 3H), 3.22 (m, 1H), 2.52 (m, 2H), 2.28 (m, 1H), 2.20 (m, 1H), 1.57 (m, 1H), 1.45 (m, 1H), 1.24 (m, 1H), 1.18 (overlap, 2H), 0.59 (m, 1H), -0.12 (m, 1H).

Example 109. 7-(3-Methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one



Step 1-7. 7-bromo-3-methyl-8-(1-(methyl-d3)-1H-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

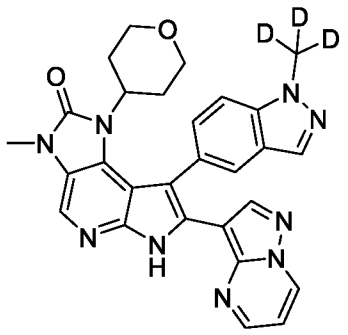


The title compound was prepared according to the procedures described in Example 91, Steps 1 to 7, using appropriately substituted starting materials. LCMS for $C_{28}H_{23}D_3BrN_6O_4S$ $(M+H)^+$: m/z = 624.1, 626.1 ; Found: 624.1, 626.1.

Step 8. 7-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-3-methyl-8-(1-(methyl-d3)-1H-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one

A solution of 7-bromo-3-methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (33.0 mg, 52.6 µmol) and 3-methoxy-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (20.0 mg, 84.0 µmol, Astateh Inc.) in dioxane/water (5:1, 2 mL) was treated with potassium carbonate (20 mg, 144.9 µmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (5 mg, 6.2 µmol) at room temperature followed by stirring at 100°C for 30 minutes. The resulted mixture was added 2 mL of MeOH and sodium hydroxide (0.5 mL, 0.9 mmol, 3 M in water) before it was stired at 60 °C for 1 hour The resulting mixture was diluted with MeOH (2 mL) and acidified with trifluoroacetic acid (TFA, 0.2 mL). The resulting mixture was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% TFA, at flow rate of 60 mL/min) to give the desired product (15.2 mg, 29.4 µmol, 55.8%) as trifluoroacetic acid salt, a white solid. LCMS for $C_{27}H_{26}D_3N_8O_3$ $(M+H)^+$: m/z = 516.3; Found: 516.2.

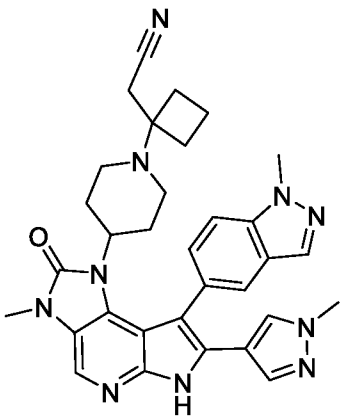
Example 110. 3-Methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-7-(pyrazolo[1,5-a]pyrimidin-3-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one



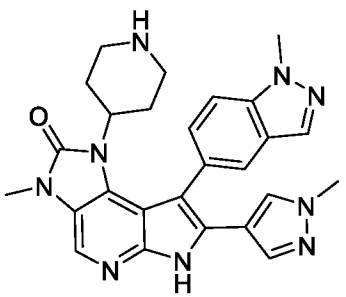
A solution of 7-bromo-3-methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-6-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one (35.0 mg, 55.9 µmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine (20.0 mg, 81.6 µmol, Astateh Inc.) in

dioxane/water (5:1, 2 mL) was treated with potassium carbonate (20 mg, 144.9 μmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (5 mg, 6.2 μmol) at room temperature followed by stirring at 100°C for 30 minutes. The resulted mixture was added 2 mL of MeOH and sodium hydroxide (0.5 mL, 0.9 mmol, 3 M in water) before it was stired at 60 °C for 1 hour The resulting mixture was diluted with MeOH (2 mL) and acidified with trifluoroacetic acid (TFA, 0.2 mL). The resulting mixture was purified via preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% TFA, at flow rate of 60 mL/min) to give the desired product (10.2 mg, 25.6 μmol, 63.6%) as trifluoroacetic acid salt, a white solid. LCMS for $C_{28}H_{23}D_3N_9O_2$ $(M+H)^+$: m/z = 523.2; Found: 523.2.

Example 111. 2-(1-(4-(3-Methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)piperidin-1-yl)cyclobutyl)acetonitrile



Step 1: 3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1-(piperidin-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one



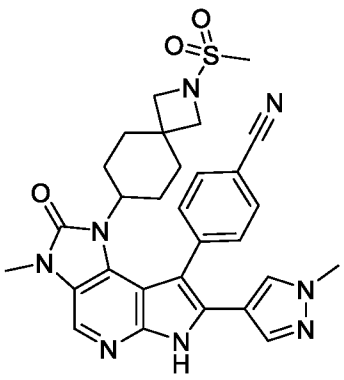
The title compound was prepared according to the procedures described in Example 101, using tert-butyl 4-aminopiperidine-1-carboxylate instead of 2-((1s,3s)-

3-aminocyclobutyl)acetonitrile, HCl salt as the starting material. LCMS calculated for: $C_{26}H_{28}N_9O$ $(M+H)^+$: m/z = 482.2; found: 482.2.

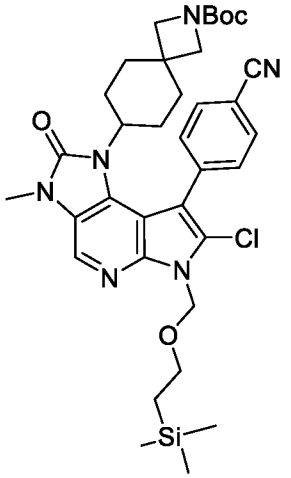
Step 2: 2-(1-(4-(3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)piperidin-1-yl)cyclobutyl)acetonitrile

To a solution of 3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-1-(piperidin-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one (25.0 mg, 0.052 mmol) in BuOH (1.0 ml) was added a solution of 2-cyclobutylideneacetonitrile (6.0 mg, 0.064 mmol) in THF (1.0 ml) followed by KOH (2.0 M, aq) (1.0 ml, 2.00 mmol). The mixture was heated to 80 °C for 6 h. After cooling to room temperature, the mixture was treated with TFA (1.0 ml). The mixture was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product as its TFA salt. LCMS calculated for $C_{32}H_{35}N_{10}O$ $(M+H)^+$: m/z = 575.3; found: 575.3.

Example 112. 4-(3-Methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-1-(2-(methylsulfonyl)-2-azaspiro[3.5]nonan-7-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile

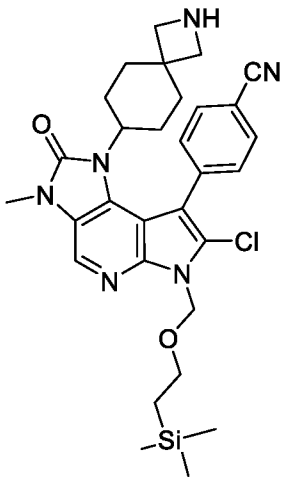


Step 1. tert-Butyl 7-(7-chloro-8-(4-cyanophenyl)-3-methyl-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)-2-azaspiro[3.5]nonane-2-carboxylate



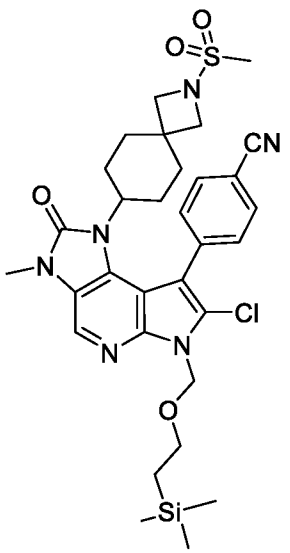
The title compound was prepared according to the procedures described in Example 104, using (4-cyanophenyl) boronic acid instead of (1-methyl-1H-indazol-5-yl)boronic acid and tert-butyl 7-(8-bromo-7-chloro-3-methyl-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)-2-azaspiro[3.5]nonane-2-carboxylate instead of tert-Butyl ((1S,3S)-3-(8-bromo-7-chloro-3-methyl-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)cyclobutyl)carbamate in Step 6. LC-MS calculated for $C_{35}H_{46}ClN_6O_4Si$ $(M+H)^+$: m/z = 677.3; found 677.3.

Step 2. 4-(7-Chloro-3-methyl-2-oxo-1-(2-azaspiro[3.5]nonan-7-yl)-6-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile



To a suspension of tert-butyl 7-(7-chloro-8-(4-cyanophenyl)-3-methyl-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2H)-yl)-2-azaspiro[3.5]nonane-2-carboxylate (97.7 mg, 0.143 mmol) in anhydrous methanol (2.04 ml) under nitrogen was added acetyl chloride (0.203 ml, 2.86 mmol). The resulting solution was stirred for 3 hours and was concentrated to residue. The residue was concentrated from acetonitrile (3x) to afford the desired product as a yellow tinted solid (85.3 mg, 96.9%). LC-MS calculated for $C_{30}H_{38}ClN_6O_2Si$ $(M+H)^+$: m/z = 577.2; found 577.2.

Step 3. 4-(7-Chloro-3-methyl-1-(2-(methylsulfonyl)-2-azaspiro[3.5]nonan-7-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile



To a solution of 4-(7-Chloro-3-methyl-2-oxo-1-(2-azaspiro[3.5]nonan-7-yl)-6-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile (42.4 mg, 0.069 mmol) in anhydrous dichloromethane (1.15 ml) was sequentially added triethylamine (0.276 mol, 0.039ml) and methanesulfonyl chloride (0.104 mmol, 12.0 mg). The resulting mixture was stirred for 30 min at ambient temperature. The reaction mixtue was diluted with 15 ml water and 30 ml of dichloromethane. The dichloromethane layer was separated and was washed with saturated sodium chloride solution. Dried over anhydrous sodium sulfate, filtered, and concentrated to afford the desired product as a tan solid (40.6 mg, 90.2%). LC-MS calculated for $C_{31}H_{40}ClN_6O_4SSi$ $(M+H)^+$: m/z = 655.2; found 655.3.

Step 4. 4-(3-Methyl-7-(1-methyl-1H-pyrazol-4-yl)-1-(2-(methylsulfonyl)-2-azaspiro[3.5]nonan-7-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile

In a microwave vial, 4-(7-Chloro-3-methyl-1-(2-(methylsulfonyl)-2-azaspiro[3.5]nonan-7-yl)-2-oxo-6-((2-(trimethylsilyl)ethoxy)methyl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile (6.77 mg, 0.010 mmol) was combined with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.37 mg, 0.026 mmol), XPhos Pd G2 (2.44 mg, 3.10 umol), cesium carbonate (10.1 mg, 0.031 mmol), and a 4:1 mixture of Dioxane water (0.276 mL / 0.069 mL). The solvent was sparged with nitrogen and heated to 70 °C for 2 hours. The reaction mixture was filtered through a 0.45 micron filter cartridge and the filtrate was concentrated dried over anhydrous sodium sulfate. Filtered and concentrated to residue. The residue was dissolved in dichloromethane (0.50 ml) and TFA was added (0.50 ml). The resulting mixture was stirred for 1 hour and concentrated. The resulting residue was dissolved in THF (0.30 ml) / methanol (0.30 m) and a 1M solution of sodium hydroxide in water was added. The resulting mixuture was stirred for 1.5 hours and was acidified with TFA (0.310 mmol, 0.024 ml), diluted with acetonitrile / methanol and was purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product as a white solid after lyophilization (3.80 mg, 53.7%). LC-MS calculated for $C_{29}H_{31}N_8O_3S$ $(M+H)^+$: m/z = 571.2; found 571.3.

Example A. JAK2 LanthaScreen JH1 Binding Assay

JAK2 JH1 binding assay utilizes catalytic domain (JH1, amino acids 826-1132) of human JAK2 expressed as N-terminal FLAG-tagged, biotinylated protein in a baculovirus expression system (Carna Biosciences, Product # 08-445-20N). The assay was conducted in black 384-well polystyrene plates in a final reaction volume of 20 µL. JAK2 JH1 (1.5 nM) was incubated with compounds (100 nL serially diluted in DMSO) in the presence of 50 nM fluorescent JAK2-JH1 tracer and 0.5 nM Streptavidin-Tb cryptate (Cisbio Part #610SATLB) in assay buffer (50 mM Tris, pH=7.5, 10 mM $MgCl_2$, 0.01% Brij-35, 0.1% BSA, 1 mM EGTA, 5% Glycerol and 5 mM DTT). Non-specific binding was accessed in the presence of 2 mM ATP. After incubation for 2 hours at 25°C, LanthaScreen signals were read on a PHERAstar FS plate reader (BMG LABTECH). Data was analyzed with IDBS XLfit and GraphPad Prism 5.0 software using a four parameter dose response curve to determine IC50 for each compound.

Example B. JAK2 LanthaScreen JH2-WT Binding Assay

JAK2 JH2-WT binding assay utilizes pseudo-kinase domain (JH2, amino-acids 536-812 with 3 surface mutations W659A, W777A, F794H) of human Wild Type JAK2 expressed as C-terminal His-Avi-tagged, biotinylated protein in a baculovirus expression system (BPS Bioscience, Catalog # 79463). The assay was conducted in black 384-well polystyrene plates in a final reaction volume of 20 µL. JAK2 JH2-WT (0.145 nM) was incubated with compounds (100 nL serially diluted in DMSO) in the presence of 50 nM Fluorescent JAK2-JH2 Tracer (MedChem Express Catalog # HY-102055) and 0.25 nM Streptavidin-Tb cryptate (Cisbio Part #610SATLB) in assay buffer (50 mM Tris, pH=7.5, 10 mM $MgCl_2$, 0.01% Brij-35, 0.1% BSA, 1 mM EGTA, 5% Glycerol and 5 mM DTT). Non-specific binding was accessed in the presence of 2 mM ATP. After incubation for 1 hour at 25°C, LanthaScreen signals were read on a PHERAstar FS plate reader (BMG LABTECH). Data was analyzed with IDBS XLfit and GraphPad Prism 5.0 software using a four parameter dose response curve to determine IC50 for each compound.

Example C. JAK2 LanthaScreen JH2-V617F Binding Assay

JAK2 JH2-V617F binding assay utilizes pseudo-kinase domain (JH2, amino-acids 536-812 with 3 surface mutations W659A, W777A, F794H) of human V617F mutant JAK2 expressed as C-terminal His-Avi-tagged, biotinylated protein in a baculovirus expression system (BPS Bioscience, Catalog # 79498). The assay was conducted in black 384-well polystyrene plates in a final reaction volume of 20 µL. JAK2 JH2-V617F (0.26 nM) was incubated with compounds (100 nL serially diluted in DMSO) in the presence of 50 nM Fluorescent JAK2-JH2 Tracer (MedChem Express Catalog # HY-102055) and 0.25 nM Streptavidin-Tb cryptate (Cisbio Part #610SATLB) in assay buffer (50 mM Tris, pH=7.5, 10 mM $MgCl_2$, 0.01% Brij-35, 0.1% BSA, 1 mM EGTA, 5% Glycerol and 5 mM DTT). Non-specific binding was accessed in the presence of 2 mM ATP. After incubation for 1 hour at 25°C, LanthaScreen signals were read on a PHERAstar FS plate reader (BMG LABTECH). Data was analyzed with IDBS XLfit and GraphPad Prism 5.0 software using a four parameter dose response curve to determine IC50 for each compound.

Example D. JAK2 HTRF Enzyme Activity Assay

JAK2 enzyme activity assays utilize catalytic domain (JH1, amino acids 808-1132) of human JAK2 expressed as N-terminal His-tagged protein in a baculovirus expression system (BPS Bioscience, Catalog # 40450). The assays was conducted in black 384-well polystyrene plates in a final reaction volume of 20 µL. JAK2 (0.015 nM) was incubated with compounds (100 nL serially diluted in DMSO) in the presence of ATP (30 µM or 1 mM) and 500 nM Biotin-labeled EQEDEPEGDYFEWLE (SEQ ID NO.: 1) peptide (BioSource International, custom synthesis) in assay buffer (50 mM Tris, pH=7.5, 10 mM $MgCl_2$, 0.01% Brij-35, 0.1% BSA, 1 mM EGTA, 5% Glycerol and 5 mM DTT) for 60 minutes at 25°C. The reactions were stopped by the addition of 10 µL of detection buffer (50 mM Tris, pH 7.8, 0.5 mg/mL BSA, 150 mM NaCl), supplemented with EDTA, LANCE Eu-W1024 anti-phosphotyrosine (PY20), (PerkinElmer, Catalog # AD0067) and Streptavidin SureLight APC (PerkinElmer Catalog # CR130-100), for a final concentration of 15 mM, 1.5 nM and 75 nM, respectively. HTRF signals were read after 30 minutes incubation at room temperature on a PHERAstar FS plate reader (BMG LABTECH).

Data was analyzed with IDBS XLfit and GraphPad Prism 5.0 software using a four parameter dose response curve to determine IC50 for each compound.

The compounds of the disclosure were tested in one or more of the assays described in Examples A-D, and the resulting data are shown in Table A.

Table A.

Example	JH1 BIND	JH2 BIND WT	JH2 BIND V617F
1	++	++	+++
2	++	++	+++
3	++	++	++
4	++	+++	+++
5	+++	+++++	+++++
6	++	+++	+++
7	++	+++	+++
8	++	++	+++
9	+++++	+++++	+++++
10	++	++	+++
11	++	++	++
12	++	++	+++
13	+++	+++++	+++++
14	+++	+++++	+++++
15	++	+++	+++
16	++++	+++++	+++++
17	+++++	+++++	+++++
18	+++	+	+
19	++	+	+
20	+++	+	+
21	+++	+	+
22	+++	++	++
23	+++	++	+++
24	++++	+	+
25	++++	+	+
26	+++++	+	+
27	+++	+	+
28	+++	+	+
29	+++	+	+
30	+++	+	+
31	+++	+	+
32	++	+	+
33	++	+	+
34	++++	++++	+++++
35	+++++	+++	+++
36	+++	+	+
37	+++++	+	+

Example	JH1 BIND	JH2 BIND WT	JH2 BIND V617F
38	+++++	++	++
39	+++++	++	++
40	+++++	++++	+++++
41	+++++	+++++	+++++
42	+++++	+++++	+++++
43	+++++	+++++	+++++
44	+++	+	+
45	++	+	++
46	++++	+	+
47	+++	+	+
48	+++++	+	+
49	+++	+	+
50	++++	+	+
51	+++++	+	+
52	+++	+	+
53	+++	+	+
54	+++	+	+
55	+++++	+	+
56	+++	+	+
57	+++	+	+
58	+++	+	++
59	+++	+	+
60	+++++	+	+
61	+++++	+	+
62	+++++	++	++
63	+++++	+	+
64	+++++	+	++
65	+++++	++	++
66	+++++	++	++
67	+++++	++	++
68	++++	+	+
69	+++++	+	+
70	+++++	+++	+++
71	++++	+	++
72	++++	+	++
73	+++++	+	+
74	++++	+	+
75	++++	+	+
76	+++++	++	++
77	+++++	++	++
78	+++++	++	++
79	+++	+	++
80	+++	+	+
81	+++++	+	++
82	+++++	+++	++++

Example	JH1 BIND	JH2 BIND WT	JH2 BIND V617F
83	+++++	+	++
84	+++++	+	+
85	+++++	+	++
86	+++++	+	++
87	+++++	+	+
88	+++++	+	++
89	++++	+	+
90	+++++	+	+
91	+++++	+	+
92	+++++	+	+
93	+++++	+	+
94	+++++	+	+
95	+++++	+	++
96	+++++	+++++	+++++
97	+++++	++	+++
98	+++++	++	++
99	+++++	++++	++++
100	++++	+++	+++
101	+++	+	+
102	++	+	+
103	+++	+	+
104	++++	+	+
105	+++++	+	+
106	+++++	+	+
107	+++	++	++
108	+++++	+	+
109	+++++	+	+
110	+++++	+	+
111	++++	+	+
112	++++	+	+

+ refers to IC_{50} of ≤ 10 nM
++ refers to IC_{50} of > 10 nM to ≤ 100 nM
+++ refers to IC_{50} of > 100 nM to ≤ 500 nM
++++ refers to IC_{50} of > 500 nM to ≤ 1000 nM
+++++ refers to IC_{50} of > 1000 nM

Example E. Cell culture and STAT5 (Tyr694) phosphorylation cell based assay

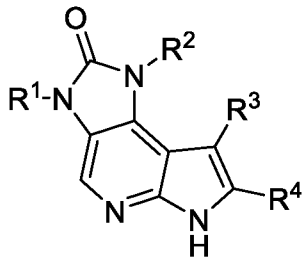
Ba/F3 cells expressing human JAK2 V617F/EPOR (mouse JAK2 WT knocked out by CRISPR) are cultured in RPMI media with 10% FBS, 1μg/mL Puromycin, 1 mg/mL Geneticin (Thermo Fisher). Ba/F3 cells expressing human JAK2 WT/EPOR are cultured in RPMI media with 10% FBS, 1 μg/mL Puromycin, 1 mg/mL Geneticin and 2 ng/mL EPO. 24 hours before the assay, the culture medium

for JAK2 V617F/EPOR Ba/F3 cells are changed to RPMI with 10% FBS without antibiotic (assay medium 1). Culture medium for Ba/F3 cells expressing human JAK2 WT/EPOR are changed to RPMI with 10% FBS and 2 ng/mL EPO (R&D systems) without antibiotic (assay medium 2). 50 nL/well test compounds in DMSO are transferred to the 384 white low volume cell culture plate (Greiner Bio-one) by ECHO liquid handler (Labcyte). The cells are centrifuged, resuspended in the corresponding fresh assay medium and dispensed at 10 μL/well (6×10^6 cells/mL) with 0.5% DMSO in the final assay. After the treated cells are incubated at 37°C, 5% CO_2 for 2 hours, 4 μL/well supplemented lysis buffer (100X blocking buffer diluted 25 fold in 4X lysis buffer, Perkin–Elmer) are added and incubated at room temperature for 60 min with gentle shaking on orbital shaker at 600 rpm. Phospho-STAT5 Cryptate antibody and Phospho-STAT5 d2 antibody (1:1 vol/vol, Perkin–Elmer) are premixed and diluted 20 fold within the detection buffer. 4 μL of the premixed antibody solution are added to each well followed with 16 hours incubation at room temperature. The product activity is determined by measuring the fluorescence at 620 nm and 665 nm on Pherastar microplate reader (BMG Labtech). A ratio is calculated (665/620nm) for each well. Wells with DMSO serve as the positive controls and wells containing high concentration of control compound are used as negative controls. IC_{50} determination is performed by fitting the curve of percent control activity versus the log of the compound concentration using the Genedata Screener software.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

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

each R^{1A} is independently selected from halo, oxo, CN, NO_2, OR^{a11}, SR^{a11}, $NHOR^{a11}$, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)NR^{c11}(OR^{a11})$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $C(=NR^{e11})R^{b11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})R^{b11}$, $NR^{c11}S(O)R^{b11}$, $NR^{c11}S(O)NR^{c11}R^{d11}$, $NR^{c11}S(O)_2R^{b11}$, $NR^{c11}S(O)(=NR^{e11})R^{b11}$, $NR^{c11}S(O)_2NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$, $OS(O)(=NR^{e11})R^{b11}$, and $OS(O)_2R^{b11}$;

each R^{a11}, R^{b11}, R^{c11}, and R^{d11} is independently selected from H, 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^{a11}, R^{b11}, R^{c11} and R^{d11} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^M 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, and C_{2-6} alkynyl;

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

each R^{2A} 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^{a21}, SR^{a21}, $NHOR^{a21}$, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)NR^{c21}(OR^{a21})$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $NR^{c21}C(O)NR^{c21}R^{d21}$, $C(=NR^{e21})R^{b21}$, $C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})NR^{c21}R^{d21}$, $NR^{c21}C(=NR^{e21})R^{b21}$, $NR^{c21}S(O)R^{b21}$, $NR^{c21}S(O)NR^{c21}R^{d21}$, $NR^{c21}S(O)_2R^{b21}$, $NR^{c21}S(O)(=NR^{e21})R^{b21}$, $NR^{c21}S(O)_2NR^{c21}R^{d21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, $S(O)_2NR^{c21}R^{d21}$, $OS(O)(=NR^{e21})R^{b21}$, $OS(O)_2R^{b21}$, SF_5, $P(O)R^{f21}R^{g21}$, $OP(O)(OR^{h21})(OR^{i21})$, $P(O)(OR^{h21})(OR^{i21})$, and $BR^{j21}R^{k21}$, 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^{2A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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, 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^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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 5-10 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, or 4 independently selected R^{2B} 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, 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^{b21} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2B} 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, 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^{f21} and R^{g21} is independently selected from H, 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^{h21} and R^{i21} 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-;

each R^{j21} and R^{k21} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j21} and R^{k21} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{2B} 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^{a22}, SR^{a22}, $NHOR^{a22}$, $C(O)R^{b22}$, $C(O)NR^{c22}R^{d22}$, $C(O)NR^{c22}(OR^{a22})$, $C(O)OR^{a22}$, $OC(O)R^{b22}$, $OC(O)NR^{c22}R^{d22}$, $NR^{c22}R^{d22}$, $NR^{c22}NR^{c22}R^{d22}$, $NR^{c22}C(O)R^{b22}$, $NR^{c22}C(O)OR^{a22}$, $NR^{c22}C(O)NR^{c22}R^{d22}$, $C(=NR^{e22})R^{b22}$, $C(=NR^{e22})NR^{c22}R^{d22}$, $NR^{c22}C(=NR^{e22})NR^{c22}R^{d22}$, $NR^{c22}C(=NR^{e22})R^{b22}$, $NR^{c22}S(O)R^{b22}$, $NR^{c22}S(O)NR^{c22}R^{d22}$, $NR^{c22}S(O)_2R^{b22}$, $NR^{c22}S(O)(=NR^{e22})R^{b22}$, $NR^{c22}S(O)_2NR^{c22}R^{d22}$, $S(O)R^{b22}$, $S(O)NR^{c22}R^{d22}$, $S(O)_2R^{b22}$, $S(O)_2NR^{c22}R^{d22}$, $OS(O)(=NR^{e22})R^{b22}$, $OS(O)_2R^{b22}$, SF_5, $P(O)R^{f22}R^{g22}$, $OP(O)(OR^{h22})(OR^{i22})$, $P(O)(OR^{h22})(OR^{i22})$, and $BR^{j22}R^{k22}$, 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^{2B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{a22}, R^{c22}, and R^{d22} 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^{a22}, R^{c22} and R^{d22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

or, any R^{c22} and R^{d22} 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, or 4 independently selected R^{2C} substituents;

each R^{b22} 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^{b22} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{2C} substituents;

each R^{e22} 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^{f22} and R^{g22} is independently selected from H, 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^{h22} and R^{i22} 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-;

each R^{j22} and R^{k22} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j22} and R^{k22} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{2C} 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^{a23}, SR^{a23}, $NHOR^{a23}$, $C(O)R^{b23}$, $C(O)NR^{c23}R^{d23}$, $C(O)NR^{c23}(OR^{a23})$, $C(O)OR^{a23}$, $OC(O)R^{b23}$, $OC(O)NR^{c23}R^{d23}$, $NR^{c23}R^{d23}$, $NR^{c23}NR^{c23}R^{d23}$, $NR^{c23}C(O)R^{b23}$, $NR^{c23}C(O)OR^{a23}$, $NR^{c23}C(O)NR^{c23}R^{d23}$, $C(=NR^{e23})R^{b23}$, $C(=NR^{e23})NR^{c23}R^{d23}$, $NR^{c23}C(=NR^{e23})NR^{c23}R^{d23}$, $NR^{c23}C(=NR^{e23})R^{b23}$, $NR^{c23}S(O)R^{b23}$, $NR^{c23}S(O)NR^{c23}R^{d23}$, $NR^{c23}S(O)_2R^{b23}$, $NR^{c23}S(O)(=NR^{e23})R^{b23}$, $NR^{c23}S(O)_2NR^{c23}R^{d23}$, $S(O)R^{b23}$, $S(O)NR^{c23}R^{d23}$, $S(O)_2R^{b23}$, $S(O)_2NR^{c23}R^{d23}$, $OS(O)(=NR^{e23})R^{b23}$, and $OS(O)_2R^{b23}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{2C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a23}, R^{c23}, and R^{d23} 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^{a23}, R^{c23} and R^{d23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c23} and R^{d23} 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^{b23} 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^{b23} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e23} 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}, $NHOR^{a3}$, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)NR^{c3}(OR^{a3})$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $C(=NR^{e3})R^{b3}$, $C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})R^{b3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)(=NR^{e3})R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, $OS(O)(=NR^{e3})R^{b3}$, $OS(O)_2R^{b3}$, SF_5, $P(O)R^{f3}R^{g3}$, $OP(O)(OR^{h3})(OR^{i3})$, $P(O)(OR^{h3})(OR^{i3})$, and $BR^{j3}R^{k3}$, 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, or 4 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-;

each R^{f3} and R^{g3} is independently selected from H, 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^{h3} and R^{i3} 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-;

each R^{j3} and R^{k3} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j3} and R^{k3} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3A} 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^{a31}, SR^{a31}, $NHOR^{a31}$, $C(O)R^{b31}$, $C(O)NR^{c31}R^{d31}$, $C(O)NR^{c31}(OR^{a31})$, $C(O)OR^{a31}$, $OC(O)R^{b31}$, $OC(O)NR^{c31}R^{d31}$, $NR^{c31}R^{d31}$, $NR^{c31}NR^{c31}R^{d31}$, $NR^{c31}C(O)R^{b31}$, $NR^{c31}C(O)OR^{a31}$, $NR^{c31}C(O)NR^{c31}R^{d31}$, $C(=NR^{e31})R^{b31}$, $C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})NR^{c31}R^{d31}$, $NR^{c31}C(=NR^{e31})R^{b31}$, $NR^{c31}S(O)R^{b31}$, $NR^{c31}S(O)NR^{c31}R^{d31}$, $NR^{c31}S(O)_2R^{b31}$, $NR^{c31}S(O)(=NR^{e31})R^{b31}$, $NR^{c31}S(O)_2NR^{c31}R^{d31}$, $S(O)R^{b31}$, $S(O)NR^{c31}R^{d31}$, $S(O)_2R^{b31}$, $S(O)_2NR^{c31}R^{d31}$, $OS(O)(=NR^{e31})R^{b31}$, $OS(O)_2R^{b31}$, SF_5, $P(O)R^{f31}R^{g31}$, $OP(O)(OR^{h31})(OR^{i31})$, $P(O)(OR^{h31})(OR^{i31})$, and $BR^{j31}R^{k31}$, 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^{3A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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, 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^{a31}, R^{c31} and R^{d31} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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 5-10 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, or 4 independently selected R^{3B} 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, 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^{b31} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3B} 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-;

each R^{f31} and R^{g31} is independently selected from H, 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^{h31} and R^{i31} 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-;

each R^{j31} and R^{k31} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j31} and R^{k31} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally

substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3B} 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^{a32}, SR^{a32}, $NHOR^{a32}$, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, $C(O)NR^{c32}(OR^{a32})$, $C(O)OR^{a32}$, $OC(O)R^{b32}$, $OC(O)NR^{c32}R^{d32}$, $NR^{c32}R^{d32}$, $NR^{c32}NR^{c32}R^{d32}$, $NR^{c32}C(O)R^{b32}$, $NR^{c32}C(O)OR^{a32}$, $NR^{c32}C(O)NR^{c32}R^{d32}$, $C(=NR^{e32})R^{b32}$, $C(=NR^{e32})NR^{c32}R^{d32}$, $NR^{c32}C(=NR^{e32})NR^{c32}R^{d32}$, $NR^{c32}C(=NR^{e32})R^{b32}$, $NR^{c32}S(O)R^{b32}$, $NR^{c32}S(O)NR^{c32}R^{d32}$, $NR^{c32}S(O)_2R^{b32}$, $NR^{c32}S(O)(=NR^{e32})R^{b32}$, $NR^{c32}S(O)_2NR^{c32}R^{d32}$, $S(O)R^{b32}$, $S(O)NR^{c32}R^{d32}$, $S(O)_2R^{b32}$, $S(O)_2NR^{c32}R^{d32}$, $OS(O)(=NR^{e32})R^{b32}$, $OS(O)_2R^{b32}$, SF_5, $P(O)R^{f32}R^{g32}$, $OP(O)(OR^{h32})(OR^{i32})$, $P(O)(OR^{h32})(OR^{i32})$, and $BR^{j32}R^{k32}$, 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^{3B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

each R^{a32}, R^{c32}, and R^{d32} 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^{a32}, R^{c32} and R^{d32} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

or, any R^{c32} and R^{d32} 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, or 4 independently selected R^{3C} substituents;

each R^{b32} 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^{b32} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{3C} substituents;

each R^{e32} 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^{f32} and R^{g32} is independently selected from H, 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^{h32} and R^{i32} 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-;

each R^{j32} and R^{k32} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j32} and R^{k32} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{3C} 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^{a33}, SR^{a33}, $NHOR^{a33}$, $C(O)R^{b33}$, $C(O)NR^{c33}R^{d33}$, $C(O)NR^{c33}(OR^{a33})$, $C(O)OR^{a33}$, $OC(O)R^{b33}$, $OC(O)NR^{c33}R^{d33}$, $NR^{c33}R^{d33}$, $NR^{c33}NR^{c33}R^{d33}$, $NR^{c33}C(O)R^{b33}$, $NR^{c33}C(O)OR^{a33}$, $NR^{c33}C(O)NR^{c33}R^{d33}$, $C(=NR^{e33})R^{b33}$, $C(=NR^{e33})NR^{c33}R^{d33}$, $NR^{c33}C(=NR^{e33})NR^{c33}R^{d33}$, $NR^{c33}C(=NR^{e33})R^{b33}$, $NR^{c33}S(O)R^{b33}$, $NR^{c33}S(O)NR^{c33}R^{d33}$, $NR^{c33}S(O)_2R^{b33}$, $NR^{c33}S(O)(=NR^{e33})R^{b33}$, $NR^{c33}S(O)_2NR^{c33}R^{d33}$, $S(O)R^{b33}$, $S(O)NR^{c33}R^{d33}$, $S(O)_2R^{b33}$, $S(O)_2NR^{c33}R^{d33}$, $OS(O)(=NR^{e33})R^{b33}$, and $OS(O)_2R^{b33}$, 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-, (4-7 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{3C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a33}, R^{c33}, and R^{d33} 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^{a33}, R^{c33} and R^{d33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c33} and R^{d33} 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^{b33} 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^{b33} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e33} 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^4 is selected from 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}, $NHOR^{a4}$, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)NR^{c4}(OR^{a4})$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $C(=NR^{e4})R^{b4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})R^{b4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)(=NR^{e4})R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $S(O)_2NR^{c4}R^{d4}$, $OS(O)(=NR^{e4})R^{b4}$, $OS(O)_2R^{b4}$, SF_5, $P(O)R^{f4}R^{g4}$, $OP(O)(OR^{h4})(OR^{i4})$, $P(O)(OR^{h4})(OR^{i4})$, and $BR^{j4}R^{k4}$, 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, or 4 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-;

each R^{f4} and R^{g4} is independently selected from H, 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^{h4} and R^{i4} 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-;

each R^{j4} and R^{k4} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j4} and R^{k4} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4A} 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^{a41}, SR^{a41}, $NHOR^{a41}$, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, $C(O)NR^{c41}(OR^{a41})$, $C(O)OR^{a41}$, $OC(O)R^{b41}$, $OC(O)NR^{c41}R^{d41}$, $NR^{c41}R^{d41}$, $NR^{c41}NR^{c41}R^{d41}$, $NR^{c41}C(O)R^{b41}$, $NR^{c41}C(O)OR^{a41}$, $NR^{c41}C(O)NR^{c41}R^{d41}$, $C(=NR^{e41})R^{b41}$, $C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})NR^{c41}R^{d41}$, $NR^{c41}C(=NR^{e41})R^{b41}$, $NR^{c41}S(O)R^{b41}$, $NR^{c41}S(O)NR^{c41}R^{d41}$, $NR^{c41}S(O)_2R^{b41}$, $NR^{c41}S(O)(=NR^{e41})R^{b41}$, $NR^{c41}S(O)_2NR^{c41}R^{d41}$, $S(O)R^{b41}$, $S(O)NR^{c41}R^{d41}$, $S(O)_2R^{b41}$, $S(O)_2NR^{c41}R^{d41}$, $OS(O)(=NR^{e41})R^{b41}$, $OS(O)_2R^{b41}$, SF_5, $P(O)R^{f41}R^{g41}$, $OP(O)(OR^{h41})(OR^{i41})$, $P(O)(OR^{h41})(OR^{i41})$, and $BR^{j41}R^{k41}$, 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^{4A} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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, 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^{a41}, R^{c41} and R^{d41} are

each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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 5-10 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, or 4 independently selected R^{4B} 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, 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^{b41} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4B} 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, 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^{f41} and R^{g41} is independently selected from H, 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^{h41} and R^{i41} 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-;

each R^{j41} and R^{k41} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j41} and R^{k41} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4B} 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^{a42}, SR^{a42}, $NHOR^{a42}$, $C(O)R^{b42}$, $C(O)NR^{c42}R^{d42}$, $C(O)NR^{c42}(OR^{a42})$, $C(O)OR^{a42}$, $OC(O)R^{b42}$, $OC(O)NR^{c42}R^{d42}$, $NR^{c42}R^{d42}$, $NR^{c42}NR^{c42}R^{d42}$, $NR^{c42}C(O)R^{b42}$, $NR^{c42}C(O)OR^{a42}$, $NR^{c42}C(O)NR^{c42}R^{d42}$, $C(=NR^{e42})R^{b42}$, $C(=NR^{e42})NR^{c42}R^{d42}$, $NR^{c42}C(=NR^{e42})NR^{c42}R^{d42}$, $NR^{c42}C(=NR^{e42})R^{b42}$, $NR^{c42}S(O)R^{b42}$, $NR^{c42}S(O)NR^{c42}R^{d42}$, $NR^{c42}S(O)_2R^{b42}$, $NR^{c42}S(O)(=NR^{e42})R^{b42}$, $NR^{c42}S(O)_2NR^{c42}R^{d42}$, $S(O)R^{b42}$, $S(O)NR^{c42}R^{d42}$, $S(O)_2R^{b42}$, $S(O)_2NR^{c42}R^{d42}$, $OS(O)(=NR^{e42})R^{b42}$, $OS(O)_2R^{b42}$, SF_5, $P(O)R^{f42}R^{g42}$, $OP(O)(OR^{h42})(OR^{i42})$, $P(O)(OR^{h42})(OR^{i42})$, and $BR^{j42}R^{k42}$, 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^{4B} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

each R^{a42}, R^{c42}, and R^{d42} 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^{a42}, R^{c42} and R^{d42} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

or, any R^{c42} and R^{d42} 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, or 4 independently selected R^{4C} substituents;

each R^{b42} 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^{b42} are each optionally substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{4C} substituents;

each R^{e42} 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^{f42} and R^{g42} is independently selected from H, 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^{h42} and R^{i42} 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-;

each R^{j42} and R^{k42} is independently selected from OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

or any R^{j42} and R^{k42} attached to the same B atom, together with the B atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group optionally

substituted with 1, 2, 3, or 4 substituents independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{4C} 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^{a43}, SR^{a43}, $NHOR^{a43}$, $C(O)R^{b43}$, $C(O)NR^{c43}R^{d43}$, $C(O)NR^{c43}(OR^{a43})$, $C(O)OR^{a43}$, $OC(O)R^{b43}$, $OC(O)NR^{c43}R^{d43}$, $NR^{c43}R^{d43}$, $NR^{c43}NR^{c43}R^{d43}$, $NR^{c43}C(O)R^{b43}$, $NR^{c43}C(O)OR^{a43}$, $NR^{c43}C(O)NR^{c43}R^{d43}$, $C(=NR^{e43})R^{b43}$, $C(=NR^{e43})NR^{c43}R^{d43}$, $NR^{c43}C(=NR^{e43})NR^{c43}R^{d43}$, $NR^{c43}C(=NR^{e43})R^{b43}$, $NR^{c43}S(O)R^{b43}$, $NR^{c43}S(O)NR^{c43}R^{d43}$, $NR^{c43}S(O)_2R^{b43}$, $NR^{c43}S(O)(=NR^{e43})R^{b43}$, $NR^{c43}S(O)_2NR^{c43}R^{d43}$, $S(O)R^{b43}$, $S(O)NR^{c43}R^{d43}$, $S(O)_2R^{b43}$, $S(O)_2NR^{c43}R^{d43}$, $OS(O)(=NR^{e43})R^{b43}$, and $OS(O)_2R^{b43}$, 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^{4C} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{a43}, R^{c43}, and R^{d43} 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^{a43}, R^{c43} and R^{d43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

or, any R^{c43} and R^{d43} 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^{b43} 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^{b43} are each optionally substituted with 1, 2, 3, or 4 independently selected R^M substituents;

each R^{e43} 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^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, 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-.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with 1, 2, or 3 independently selected R^{1A} substituents.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently selected from halo, CN, NO_2, OR^{a11}, and SR^{a11}, wherein each R^{a11} is independently selected from H and C_{1-6} alkyl.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from H, methyl, ethyl, and hydroxyethyl.

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

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

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

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein each R^{2A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21},

$C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

10. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein each R^{2A} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)R^{b21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1 or 2 independently selected R^{2B} substituents.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein 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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

wherein each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein each R^{a21}, R^{c21}, and R^{d21} is independently selected from H and C_{1-6} alkyl;

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

wherein each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents.

13. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein each R^{2A} is independently selected from methyl, cyclobutyl, methoxy, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl, wherein each cyclobutyl of R^{2A} is optionally substituted by one R^{2B} substituent which is C_{1-6} alkyl, and wherein the C_{1-6} alkyl of R^{2B} is optionally substituted by cyano.

14. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups independently selected from methyl, cyanomethylcyclobutyl, methoxy, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfony.

15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein 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-, 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^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents.

16. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from H, 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_{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, or 4 independently selected R^{3A} substituents.

17. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from H, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents.

18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein each R^{3A} is independently selected from 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^{a31}, $C(O)R^{b31}$, SR^{a31}, SO_2R^{b31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

19. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein each R^{3A} 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-, CN, OR^{a31}, $C(O)R^{b31}$, and SO_2R^{b31}, wherein the C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, and C_{6-10} aryl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

20. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein each R^{3A} is independently selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, $C(O)R^{b31}$, SO_2R^{b31}, and OR^{a31}, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents, and wherein each R^{a31} and R^{b31} is independently selected from H and C_{1-6} alkyl.

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$, wherein each phenyl and 4-6 membered heterocycloalkyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$.

22. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein each R^{3B} is independently selected from phenyl, 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$;

each R^{a32} is independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl; and

each R^{b32} is independently selected from H and C_{1-6} alkyl.

23. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein each R^{3B} is independently selected from phenyl, morpholinyl, CN, tetrahydropyranyloxy, methylcarbonyl, and C(O)OH.

24. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from H, ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl, wherein the ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl are each optionally substituted by one or two R^{3A} groups independently selected from methyl, trideuteromethyl, phenyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, methylcarbonyl, and methylsulfonyl, wherein the methyl group of the methylcarbonyl is substituted by methylsulfonylphenyl.

25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents.

26. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl,

C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, of R^4 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4A} substituents.

27. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents.

28. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^{4A} is independently selected from 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, OR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents.

29. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^{4A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents; wherein each R^{a41} is independently

selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl; and wherein each R^{b41} is independently selected from H and C_{1-6} alkyl.

30. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each R^{4A} is independently selected from fluoro, methyl, cyano, hydroxy, methoxy, N,N-dimethylaminocarbonyl, ethyl, 2-methylpropyl, difluoroethyl, hydroxy, cyano, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl are each optionally substituted by 1 or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl.

31. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl;

wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1

or 2 R^{4B} substituents independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl, wherein each R^{a42} is independently selected from H, and C_{1-6} alkyl.

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

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

R^2 is selected from H, 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-, 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^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, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{3A} is independently selected from 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^{a31}, SR^{a31}, SO_2R^{b31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents; and

each R^{4A} is independently selected from 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, OR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents.

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

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

R^2 is selected from H, 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-, 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^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, C_{3-10} cycloalkyl, CN, NO_2, OR^{a21}, SR^{a21}, $C(O)R^{b21}$, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $OC(O)R^{b21}$, $OC(O)NR^{c21}R^{d21}$, $NR^{c21}R^{d21}$, $NR^{c21}C(O)R^{b21}$, $S(O)R^{b21}$, $S(O)NR^{c21}R^{d21}$, $S(O)_2R^{b21}$, and $S(O)_2NR^{c21}R^{d21}$, wherein the C_{1-6} alkyl of R^{2A} is optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

each R^{2B} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2, wherein each C_{1-6} alkyl of R^{2B} is optionally substituted by cyano;

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

each R^{3A} is independently selected from 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^{a31}, SR^{a31}, SO_2R^{b31}, and $NR^{c31}R^{d31}$, 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^{3A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents;

each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of each R^{a31}, R^{b31}, R^{c31}, and R^{d31} is optionally substituted with 1, 2, 3, or 4 independently selected R^{3B} substituents.

each R^{3B} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 4-6 membered heterocycloalkyl, CN, NO_2, OR^{a32}, SR^{a32}, $C(O)R^{b32}$, $C(O)NR^{c32}R^{d32}$, and $C(O)OR^{a32}$, wherein each phenyl and 4-6 membered heterocycloalkyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$;

R^4 is selected from 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}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$, 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, or 4 independently selected R^{4A} substituents; and

each R^{4A} is independently selected from 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, OR^{a41}, $C(O)R^{b41}$, $C(O)NR^{c41}R^{d41}$, and $C(O)OR^{a41}$, 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^{4A} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{4B} substituents;

each R^{a41}, R^{b41}, 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, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

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

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-6 membered heterocycloalkyl, and (5-6 membered heteroaryl)-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 C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, and $NR^{c21}C(O)R^{b21}$;

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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

R^3 is selected from H, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10

membered heteroaryl, 4-10 membered heterocycloalkyl of R^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents;

each R^{3A} is independently selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, OR^{a31}, and SO_2R^{b31}, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents;

each R^{a31} is independently selected from H and C_{1-6} alkyl;

each R^{b31} is independently selected from H and C_{1-6} alkyl;

each R^{3B} is independently selected from 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$;

each R^{a32} is independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl;

each R^{b32} is independently selected from H and C_{1-6} alkyl;

R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents;

each R^{4A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, and $C(O)R^{b41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents;

each R^{a41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^{b41} is independently selected from H and C_{1-6} alkyl;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

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

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (6-10 membered heterocycloalkyl)-C_{1-6} alkyl-, wherein the C_{1-6} alkyl, phenyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 6-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (6-10 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 C_{1-6} alkyl, C_{3-10} cycloalkyl, OR^{a21}, $C(O)NR^{c21}R^{d21}$, $C(O)OR^{a21}$, $NR^{c21}C(O)R^{b21}$, $NR^{c21}C(O)OR^{a21}$, and $S(O)R^{b21}$, wherein the C_{1-6} alkyl and C_{3-10} cycloalkyl of R^{2A} are each optionally substituted with 1 or 2 independently selected R^{2B} 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, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{a21}, R^{c21} and R^{d21} are each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

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

each R^{b21} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is each optionally substituted with 1, 2, 3, or 4 independently selected R^{2B} substituents;

each R^{2B} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, and NO_2, wherein each C_{1-6} alkyl of R^{2B} is optionally substituted by cyano;

R^3 is selected from H, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{2-6} alkynyl, C_{6-10} aryl,

C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^3 are each optionally substituted with 1, 2, 3, or 4 independently selected R^{3A} substituents;

each R^{3A} is independently selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, CN, $C(O)R^{b31}$, SO_2R^{b31}, and OR^{a31}, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and phenyl-C_{1-6} alkyl- of R^{3A} are each optionally substituted with 1 or 2 independently selected R^{3B} substituents;

each R^{a31} and R^{b31} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of each R^{a31} and R^{b31} is optionally substituted with 1 or 2 independently selected R^{3B} substituents;

each R^{3B} is independently selected from phenyl, 4-6 membered heterocycloalkyl, CN, OR^{a32}, $C(O)R^{b32}$, and $C(O)OR^{a32}$, wherein each phenyl of R^{3B} is optionally substituted with $S(O)_2R^{b33}$;

each R^{a32} is independently selected from H, C_{1-6} alkyl, and 4-6 membered heterocycloalkyl;

each R^{b32} is independently selected from H and C_{1-6} alkyl;

R^4 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, C_{3-6} cycloalkyl-C_{1-6} alkyl-, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, and $S(O)_2R^{b4}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, phenyl-C_{1-6} alkyl-, and C_{3-6} cycloalkyl-C_{1-6} alkyl- of R^4 are each optionally substituted with 1 or 2 independently selected R^{4A} substituents;

each R^{b4}, 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, and C_{3-6} cycloalkyl;

each R^{4A} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-6} alkyl-, CN, OR^{a41}, $C(O)R^{b41}$, and $C(O)NR^{c41}R^{d41}$, wherein the C_{1-6} alkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, (5-6 membered heteroaryl)-C_{1-6} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-6} alkyl- of R^{4A} are each optionally substituted with 1 or 2 independently selected R^{4B} substituents;

each R^{a41} is independently selected from H, C_{1-6} alkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^{b41} is independently selected from H and C_{1-6} alkyl;

each R^{c41} and R^{d41} is independently selected from H and C_{3-6} cycloalkyl;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

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

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, azabicyclo[3.2.1]octanyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, piperidinyl, azaspiro[3.5]nonanyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups;

each R^{2A} is independently selected from methyl, cyclobutyl, methoxy, ethylamido, methoxyethylamido, piperidinylcarbonyl, cyanomethyl, methoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methylaminocarbonyl, and methylsulfonyl, wherein each cyclobutyl of R^{2A} is optionally substituted by one R^{2B} substituent which is C_{1-6} alkyl, and wherein the C_{1-6} alkyl of R^{2B} is optionally substituted by cyano;

R^3 is selected from H, ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl, wherein the ethynyl, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl,

pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, piperidinyl, and pyridyl are each optionally substituted by one or two R^{3A} groups;

each R^{3A} is independently selected from methyl, trideuteromethyl, phenyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, methylcarbonyl, and methylsulfonyl, wherein the methyl group of the methylcarbonyl is substituted by methylsulfonylphenyl;

R^4 is selected from ethyl, hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, cyclopropylaminocarbonyl, and methylsulfonyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, pyridyl, pyrazolo[1,5-a]pyrimidinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, cyclopropylmethyl, phenylmethyl, and cyclopropylaminocarbonyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents;

each R^{4A} is independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, hydroxy, cyano, methoxy, N,N-dimethylaminocarbonyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents;

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

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

R^1 is selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl of R^1 is optionally substituted with OH;

R^2 is selected from H, methyl, isopropyl, isobutyl, tert-butyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl, wherein the cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, phenyl, tetrahydropyranyl, pyridyl, benzofuranyl, and pyrazolylmethyl are each optionally substituted with 1 or 2 R^{2A} groups;

each R^{2A} is independently selected from methyl, methoxy, ethylamido, methoxyethylamido, and piperidinylcarbonyl;

R^3 is selected from H, phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazoyl, indazolyl, and pyridyl, wherein the phenyl, cyclohexenyl, pyrazolyl, cyclopropyl, dihydropyranyl, azabicyclo[4.1.0]heptanyl, dihydroindenyl, imidazopyridinyl, pyrrolo[1,2-a]pyrazinyl, tetrahydrothieno[3,2-c]pyridinyl, thieno[3,2-c]pyridinyl, isoquinolinyl, benzothiazolyl, chromanyl, thiazolyl, indazolyl, and pyridyl are each optionally substituted by one or two R^{3A} groups;

each R^{3A} is independently selected from methyl, cyano, hydroxy, methoxy, cyclopropyl, cyanocyclopropyl, morpholinyl, morpholinylcyclopropyl, piperazinyl, methylcarbonylpiperazinyl, tetrahydropyranyloxymethyl, benzyl, carboxybenzyl, and methylsulfonyl;

R^4 is selected from hydroxyethyl, isopropylcarbonyl, phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl, wherein the phenyl, cyclopropyl, piperidinyl, dihydropyranyl, pyrazolyl, cyclohexenyl, and pyridyl of R^4 are optionally substituted by 1 or 2 R^{4A} substituents;

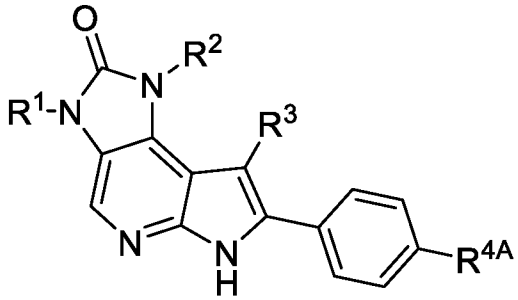
each R^{4A} is independently selected from CN, fluoro, methyl, ethyl, difluoroethyl, 2-methylpropyl, piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, isopropylcarbonyl, piperidinylmethyl, pyridyloxy, tetrahydropyranyloxy, isopropoxy, methoxy, and pyridylmethyl, wherein the methyl, ethyl, 2-methylpropyl,

piperidinyl, piperazinyl, tetrahydrothiophene 1,1-dioxide, piperidinylmethyl, pyridyloxy, tetrahydropyranoxy, isopropoxy, methoxy, and pyridylmethyl of R^{4A} are each optionally substituted by 1 or 2 R^{4B} substituents; and

each R^{4B} is independently selected from C_{1-6} alkyl, OR^{a42}, C_{1-6} alkylsulfonyl, di(C_{1-6} alkyl)amino, and C_{1-6} alkylcarbonyl, wherein the di(C_{1-6} alkyl)amino is optionally substituted with C_{1-6} alkylsulfonyl; and

each R^{a42} is independently selected from H and C_{1-6} alkyl.

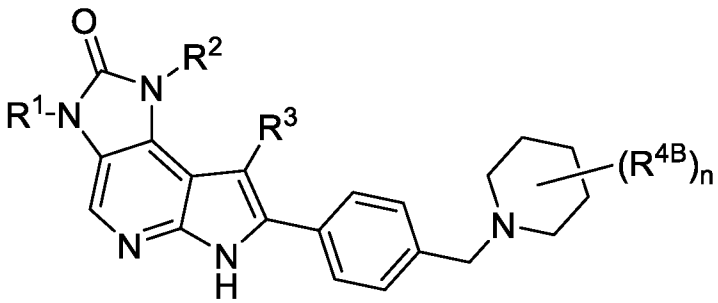
38. The compound of claim 1, wherein the compound of Formula I is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof.

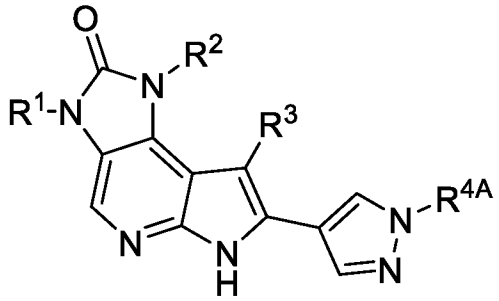
39. The compound of claim 1, wherein the compound of Formula I is a compound of Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, 2, 3, or 4.

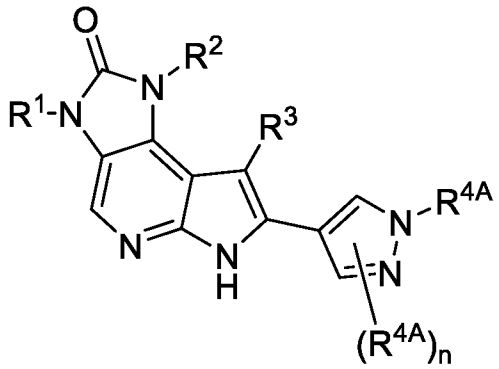
40. The compound of claim 1, wherein the compound of Formula I is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof.

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



IV

or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, or 2.

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

3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(benzofuran-5-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-(2-hydroxyethyl)-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-1H-pyrazol-4-yl)-3-methyl-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-methyl-7-(4-((methyl(3-(methylsulfonyl)propyl)amino)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(3-fluoro-4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3-methyl-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-(4-ethylpiperazin-1-yl)phenyl)-3-methyl-1-(pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclohexyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(tert-butyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclohexyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-ethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-methyl-7-(1-methyl-1H-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-(tetrahydro-2H-pyran-3-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-(4-ethylpiperazin-1-yl)phenyl)-3-methyl-1-((1-methyl-1H-pyrazol-4-yl)methyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(4-(4-ethylpiperazin-1-yl)phenyl)-3-methyl-1-(2-oxo-2-(piperidin-1-yl)ethyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclohexyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-isobutyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclobutyl-8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-1-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(4-methoxyphenyl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(tert-butyl)-8-(4-methoxycyclohex-1-en-1-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

4-(1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

1-(4-(1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

4-((4-(1-isopropyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)-1H-pyrazol-1-yl)methyl)benzoic acid;

1-cyclopentyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclopentyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-(4-(1-cyclopentyl-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

1-(4-(1-cyclopentyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

1-cyclopentyl-8-(4-methoxycyclohex-1-en-1-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-cyclopentyl-8-(3,6-dihydro-2H-pyran-4-yl)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-cyclopropyl-1,3-dimethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(6-methoxypyridin-3-yl)-1,3-dimethyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

4-(1-isopropyl-3-methyl-2-oxo-7-(1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl)-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

4-(7-(4-(4-acetylpiperazin-1-yl)phenyl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

4-(7-(3,6-dihydro-2H-pyran-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

4-(7-(3,6-dihydro-2H-pyran-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-8-yl)benzonitrile;

1,3-dimethyl-8-phenyl-7-(pyridin-3-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1,3-dimethyl-8-phenyl-7-(piperidin-4-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(2-hydroxyethyl)-1,3-dimethyl-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-isobutyryl-1,3-dimethyl-8-phenyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

1-isopropyl-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-(bicyclo[2.2.1]heptan-2-yl)-3-methyl-7-(1-((methylsulfonyl)methyl)-1*H*-pyrazol-4-yl)-8-phenyl-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one; and

3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

or a pharmaceutically acceptable salt thereof.

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

1-cyclopentyl-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-(4-(3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

1-(4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)phenyl)cyclopropane-1-carbonitrile;

7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(4-(1-morpholinocyclopropyl)phenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(1-(2,2-difluoroethyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(thieno[3,2-*c*]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

(*S*)-3-methyl-7-(4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenyl)-8-phenyl-1-(tetrahydro-2*H*-pyran-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-8-(4-methoxyphenyl)-3-methyl-7-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyridin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-isopropyl-7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(6-methoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-(6-isopropoxypyridin-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(6-((tetrahydro-2*H*-pyran-4-yl)oxy)pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(6-(pyridin-3-yloxy)pyridin-3-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-cyclopropyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(cyclohex-1-en-1-yl)-1-cyclopentyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one;

1-cyclopentyl-7-(2-hydroxyethyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-7-cyclopropyl-3-methyl-8-(thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-b]pyridin-2(1*H*)-one;

2-(1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)cyclopropane-1-carbonitrile;

N-(4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)-2-methoxyacetamide;

N-(4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-1(2*H*)-yl)cyclohexyl)acetamide;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(2-morpholinothiazol-5-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-8-(isoquinolin-6-yl)-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(benzo[d]thiazol-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(chroman-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(6-(piperazin-1-yl)thieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(6-(4-acetylpiperazin-1-yl)thieno[3,2-c]pyridin-2-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(5-(methylsulfonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(3-methylpyrrolo[1,2-a]pyrazin-7-yl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-8-(imidazo[1,5-a]pyridin-7-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

8-(1-hydroxy-2,3-dihydro-1H-inden-5-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-8-(4-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)phenyl)-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one; and

8-(3-azabicyclo[4.1.0]heptan-6-yl)-7-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-1-isopropyl-3-methyl-3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one;

or a pharmaceutically acceptable salt thereof.

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

4-(1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)-N,N-dimethylbenzamide;

3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(pyrazolo[1,5-*a*]pyrimidin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1H)-one;

7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

7-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

methyl (1*S*)-3-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate;

(1*S*)-3-(7-(4-methoxyphenyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)-N-methyl-8-azabicyclo[3.2.1]octane-8-carboxamide;

7-(cyclopropyl(hydroxy)methyl)-3-methyl-8-(1-methyl-1H-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

4-((1-isopropyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-7-yl)methyl)benzonitrile;

1-cyclopentyl-7-ethyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-cyclopentyl-N-cyclopropyl-3-methyl-8-(1-methyl-1H-indazol-5-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxamide;

1-cyclopentyl-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(methylsulfonyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

1-isopropyl-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-8-(phenylethynyl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-b]pyridin-2(1*H*)-one;

2-((1*S*,3*S*)-3-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)acetonitrile;

2-((1*S*,4*S*)-4-(3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile;

2-((1*S*,4*S*)-4-(7-(1-(2-hydroxy-2-methylpropyl)-1*H*-pyrazol-4-yl)-3-methyl-8-

(1-methyl-1H-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile;

methyl ((1*S*,3*S*)-3-(3-methyl-8-(1-methyl-1H-indazol-5-yl)-7-(1-methyl-1H-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2H)-yl)cyclobutyl)carbamate;

ethyl ((1*S*,3*S*)-3-(8-(4-cyanophenyl)-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate;

ethyl ((1*S*,3*S*)-3-(8-(4-methoxyphenyl)-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclobutyl)carbamate;

1-isopropyl-3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-8-(1-(2-(4-(methylsulfonyl)phenyl)acetyl)piperidin-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

2-((1*S*,4*S*)-4-(7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)cyclohexyl)acetonitrile;

7-(3-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

3-methyl-8-(1-(methyl-*d*3)-1*H*-indazol-5-yl)-7-(pyrazolo[1,5-a]pyrimidin-3-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2(1*H*)-one;

2-(1-(4-(3-methyl-8-(1-methyl-1*H*-indazol-5-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-2-oxo-3,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(2*H*)-yl)piperidin-1-yl)cyclobutyl)acetonitrile; and

4-(3-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-1-(2-(methylsulfonyl)-2-azaspiro[3.5]nonan-7-yl)-2-oxo-1,2,3,6-tetrahydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-8-yl)benzonitrile;

or a pharmaceutically acceptable salt thereof.

45. The compound of any one of claims 1 to 44, or a pharmaceutically acceptable salt thereof, wherein the compound is deuterated.

46. A pharmaceutical composition, comprising a compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

47. A method of inhibiting an activity of the V617F variant of JAK2 kinase, comprising contacting the kinase with a compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof.

48. A method of treating cancer in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof.

49. The method of claim 48, wherein the cancer is selected from bladder cancer, breast cancer, cervical cancer, colorectal cancer, cancer of the small intestine, colon cancer, rectal cancer, cancer of the anus, endometrial cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, vulvar cancer, esophageal cancer, gall bladder cancer, pancreatic cancer, stomach cancer, thyroid cancer, parathyroid cancer, neuroendocrine cancer, skin cancer, and brain cancer.

50. The method of claim 48, wherein the cancer is a hematological cancer.

51. The method of claim 48, wherein the cancer is selected from leukemia, lymphoma, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, acute myeloid leukemia, B-cell lymphoma, cutaneous T-cell lymphoma, acute myelogenous leukemia, Hodgkin’s or non-Hodgkin’s lymphoma, a myeloproliferative neoplasm), myelodysplastic syndrome, chronic eosinophilic leukemia, Waldenstrom's Macroglubulinemia, hairy cell lymphoma, chronic myelogenic lymphoma, acute lymphoblastic lymphoma, AIDS-related lymphoma, and Burkitt's lymphoma.

52. A method of treating a myeloproliferative disorder in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof.

53. The method of claim 52, wherein the myeloproliferative disorder is selected from polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, primary myelofibrosis, post- essential thrombocythemia myelofibrosis, post polycythemia vera myelofibrosis, chronic myelogenous leukemia, chronic myelomonocytic leukemia, hypereosinophilic syndrome, and systemic mast cell disease.

54. A method of treating myelodysplastic syndrome in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof.