(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
08 March 2018 (08.03.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/044783 A1

(51) International Patent Classification:
C07D 403/12 (2006.01) *C07D 417/06* (2006.01)
C07D 233/90 (2006.01) *C07D 417/14* (2006.01)
C07D 403/06 (2006.01) *C07D 263/34* (2006.01)
C07D 405/12 (2006.01) *C07D 277/56* (2006.01)

(21) International Application Number:
PCT/US2017/048880

(22) International Filing Date:
28 August 2017 (28.08.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/380,599 29 August 2016 (29.08.2016) US

(71) Applicant: **INCYTE CORPORATION** [US/US]; 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US).

(72) Inventor; and
(71) Applicant: **MEI, Song** [CN/US]; Incyte Corporation, 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US).

(72) Inventors: **WU, Liangxing**; Incyte Corporation, 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US). **ZHANG, Fenglei**; Incyte Corporation, 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US). **YAO, Wenqing**; Incyte Corporation, 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US).

(74) Agent: **KING, Annie J.** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

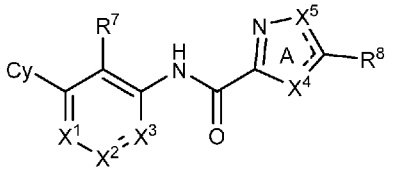
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2018/044783 A1

(54) Title: HETEROCYCLIC COMPOUNDS AS IMMUNOMODULATORS



(I)

(57) Abstract: Disclosed are compounds of Formula (I), methods of using the compounds as immunomodulators, and pharmaceutical compositions comprising such compounds. The compounds are useful in treating, preventing or ameliorating diseases or disorders such as cancer or infections.

HETEROCYCLIC COMPOUNDS AS IMMUNOMODULATORS

FIELD OF THE INVENTION

The present application is concerned with pharmaceutically active compounds. The disclosure provides compounds as well as their compositions and methods of use. The compounds modulate PD-1/PD-L1 protein/protein interaction and are useful in the treatment of various diseases including infectious diseases and cancer.

BACKGROUND OF THE INVENTION

The immune system plays an important role in controlling and eradicating diseases such as cancer. However, cancer cells often develop strategies to evade or to suppress the immune system in order to favor their growth. One such mechanism is altering the expression of co-stimulatory and co-inhibitory molecules expressed on immune cells (Postow et al, J. Clinical Oncology 2015, 1-9). Blocking the signaling of an inhibitory immune checkpoint, such as PD-1, has proven to be a promising and effective treatment modality.

Programmed cell death-1 (PD-1), also known as CD279, is a cell surface receptor expressed on activated T cells, natural killer T cells, B cells, and macrophages (Greenwald et al, Annu. Rev. Immunol 2005, 23:515–548; Okazaki and Honjo, Trends Immunol 2006, (4):195-201). It functions as an intrinsic negative feedback system to prevent the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance. In addition, PD-1 is also known to play a critical role in the suppression of antigen-specific T cell response in diseases like cancer and viral infection (Sharpe et al, *Nat Immunol* 2007 8, 239–245; Postow et al, J. Clinical Oncol 2015, 1-9).

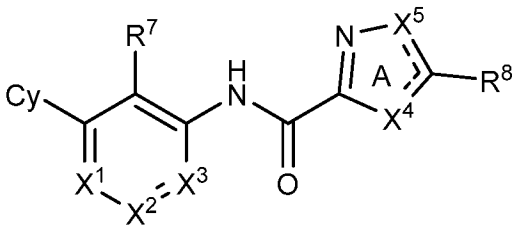
The structure of PD-1 consists of an extracellular immunoglobulin variable-like domain followed by a transmembrane region and an intracellular domain (Parry et al, Mol Cell Biol 2005, 9543–9553). The intracellular domain contains two phosphorylation sites located in an immunoreceptor tyrosine-based inhibitory motif and an immunoreceptor tyrosine-based switch motif, which suggests that PD-1 negatively regulates T cell receptor-mediated signals. PD-1 has two ligands, PD-L1 and PD-L2 (Parry et al, Mol Cell Biol 2005, 9543–9553; Latchman et al, Nat Immunol 2001, 2, 261–268), and they differ in their expression patterns. PD-L1 protein is upregulated on macrophages and dendritic cells in response to lipopolysaccharide and GM-CSF treatment, and on T cells and B cells upon T cell receptor and B cell receptor signaling. PD-L1 is also highly expressed on almost all tumor cells, and the expression is further increased after IFN-γ treatment (Iwai et al,

PNAS2002, 99(19):12293-7; Blank et al, Cancer Res 2004, 64(3):1140-5). In fact, tumor PD-L1 expression status has been shown to be prognostic in multiple tumor types (Wang et al, Eur J Surg Oncol 2015; Huang et al, Oncol Rep 2015; Sabatier et al, Oncotarget 2015, 6(7): 5449–5464). PD-L2 expression, in contrast, is more restricted and is expressed mainly by dendritic cells (Nakae et al, J Immunol 2006, 177:566-73). Ligation of PD-1 with its ligands PD-L1 and PD-L2 on T cells delivers a signal that inhibits IL-2 and IFN-γ production, as well as cell proliferation induced upon T cell receptor activation (Carter et al, Eur J Immunol 2002, 32(3):634-43; Freeman et al, J Exp Med 2000, 192(7):1027-34). The mechanism involves recruitment of SHP-2 or SHP-1 phosphatases to inhibit T cell receptor signaling such as Syk and Lck phosphorylation (Sharpe et al, Nat Immunol 2007, 8, 239–245). Activation of the PD-1 signaling axis also attenuates PKC-θ activation loop phosphorylation, which is necessary for the activation of NF-κB and AP1 pathways, and for cytokine production such as IL-2, IFN-γ and TNF (Sharpe et al, Nat Immunol 2007, 8, 239–245; Carter et al, Eur J Immunol 2002, 32(3):634-43; Freeman et al, J Exp Med 2000, 192(7):1027-34).

Several lines of evidence from preclinical animal studies indicate that PD-1 and its ligands negatively regulate immune responses. PD-1-deficient mice have been shown to develop lupus-like glomerulonephritis and dilated cardiomyopathy (Nishimura et al, Immunity 1999, 11:141–151; Nishimura et al, Science 2001, 291:319–322). Using an LCMV model of chronic infection, it has been shown that PD-1/PD-L1 interaction inhibits activation, expansion and acquisition of effector functions of virus-specific CD8 T cells (Barber et al, Nature 2006, 439, 682-7). Together, these data support the development of a therapeutic approach to block the PD-1-mediated inhibitory signaling cascade in order to augment or "rescue" T cell response. Accordingly, there is a need for new compounds that block PD-1/PD-L1 protein/protein interaction.

SUMMARY

The present disclosure provides, *inter alia*, a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein constituent variables are defined herein.

The present disclosure further provides a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt or a stereoisomer thereof, and at least one pharmaceutically acceptable carrier or excipient.

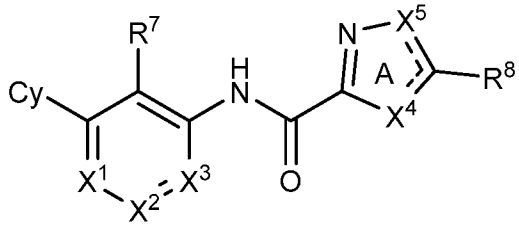
The present disclosure further provides methods of modulating or inhibiting PD-1/PD-L1 protein/protein interaction, which comprises administering to an individual a compound of the disclosure, or a pharmaceutically acceptable salt or a stereoisomer thereof.

The present disclosure further provides methods of treating a disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of a compound of the disclosure, or a pharmaceutically acceptable salt or a stereoisomer thereof.

DETAILED DESCRIPTION

I. Compounds

Provided herein is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10}cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$,

$OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, $-P(O)R^{10}R^{10}$, $-P(O)(OR^{10})(OR^{10})$, $-B(OH)_2$, $-B(OR^{10})_2$ and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aC(=NOH)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from B, P, N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, $-P(O)R^{11}R^{11}$, $-P(O)(OR^{11})(OR^{11})$, $-B(OH)_2$, $-B(OR^{11})_2$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, ethyl, propyl, isopropyl, butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, $-P(O)R^{11}R^{11}$, $-P(O)(OR^{11})(OR^{11})$, $-B(OH)_2$, $-B(OR^{11})_2$, or $S(O)_2NR^{11}R^{11}$, wherein the butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4}

alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{5-6} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered

heterocycloalkyl)-C_{1-4} alkyl- of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^c 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of

R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $NR^gC(=NOH)NR^gR^g$, $NR^gC(=NCN)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, $-P(O)R^gR^g$, $-P(O)(OR^g)(OR^g)$, $-B(OH)_2$, $-B(OR^g)_2$ and $S(O)_2NR^gR^g$; wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, $NR^oC(O)OR^o$, $C(=NR^o)NR^oR^o$, $NR^oC(=NR^o)NR^oR^o$, $S(O)R^o$, $S(O)NR^oR^o$, $S(O)_2R^o$, $NR^oS(O)_2R^o$, $NR^oS(O)_2NR^oR^o$, $-P(O)R^oR^o$, $-P(O)(OR^o)(OR^o)$, $-B(OH)_2$, $-B(OR^o)_2$ and $S(O)_2NR^oR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, $-P(O)R^eR^e$, $-P(O)(OR^e)(OR^e)$, $-B(OH)_2$, $-B(OR^e)_2$ and $S(O)_2NR^eR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, $NR^rC(O)R^r$, $NR^rC(O)NR^rR^r$, $NR^rC(O)OR^r$, $C(=NR^r)NR^rR^r$, $NR^rC(=NR^r)NR^rR^r$, $NR^rC(=NOH)NR^rR^r$, $NR^rC(=NCN)NR^rR^r$, $S(O)R^r$, $S(O)NR^rR^r$, $S(O)_2R^r$, $NR^rS(O)_2R^r$, $NR^rS(O)_2NR^rR^r$, $-P(O)R^rR^r$, $-P(O)(OR^r)(OR^r)$, $-B(OH)_2$, $-B(OR^r)_2$ and $S(O)_2NR^rR^r$, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{6-10} aryl-C_{1-4} alkyl-, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NHR^i, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $NR^iC(=NOH)NR^iR^i$, $NR^iC(=NCN)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$,

$NR^iS(O)_2NR^iR^i$, $-P(O)R^iR^i$, $-P(O)(OR^i)(OR^i)$, $-B(OH)_2$, $-B(OR^i)_2$ and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, $-P(O)R^kR^k$, $-P(O)(OR^k)(OR^k)$, $-B(OH)_2$, $-B(OR^k)_2$ and $S(O)_2NR^kR^k$, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl, taken together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^q substituents;

or any two R^k substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally

substituted with 1, 2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^q substituents;

or any two R^o substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^{10} substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^{11} substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^q are each optionally substituted with halo, OH, CN, -COOH, NH_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10}cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, $-P(O)R^{10}R^{10}$, $-P(O)(OR^{10})(OR^{10})$, $-B(OH)_2$, $-B(OR^{10})_2$ and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aC(=NOH)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from B, P, N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, $-P(O)R^{11}R^{11}$, $-P(O)(OR^{11})(OR^{11})$, $-B(OH)_2$, $-B(OR^{11})_2$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, ethyl, propyl, isopropyl, butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, $-P(O)R^{11}R^{11}$, $-P(O)(OR^{11})(OR^{11})$, $-B(OH)_2$, $-B(OR^{11})_2$, or $S(O)_2NR^{11}R^{11}$, wherein the butyl, 2-butyl, 2-

methylpropyl, C_{5-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{5-6} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2,

$NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^c 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $NR^gC(=NOH)NR^gR^g$, $NR^gC(=NCN)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, $-P(O)R^gR^g$, $-P(O)(OR^g)(OR^g)$, $-B(OH)_2$, $-B(OR^g)_2$ and $S(O)_2NR^gR^g$; wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, $NR^oC(O)OR^o$, $C(=NR^o)NR^oR^o$, $NR^oC(=NR^o)NR^oR^o$, $S(O)R^o$, $S(O)NR^oR^o$, $S(O)_2R^o$, $NR^oS(O)_2R^o$, $NR^oS(O)_2NR^oR^o$, $-P(O)R^oR^o$, $-P(O)(OR^o)(OR^o)$, $-B(OH)_2$, $-B(OR^o)_2$ and $S(O)_2NR^oR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, $-P(O)R^eR^e$, $-P(O)(OR^e)(OR^e)$, $-B(OH)_2$,

-B(OR^e)$_2$ and S(O)$_2$NR^eR^e, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, NHOR^r, OR^r, SR^r, C(O)R^r, C(O)NR^rR^r, C(O)OR^r, OC(O)R^r, OC(O)NR^rR^r, NHR^r, NR^rR^r, NR^rC(O)R^r, NR^rC(O)NR^rR^r, NR^rC(O)OR^r, C(=NR^r)NR^rR^r, NR^rC(=NR^r)NR^rR^r, NR^rC(=NOH)NR^rR^r, NR^rC(=NCN)NR^rR^r, S(O)R^r, S(O)NR^rR^r, S(O)$_2$$R^r$, N$R^r$S(O)$_2$$R^r$, N$R^r$S(O)$_2NR^rR^r$, -P(O)$R^rR^r$, -P(O)($OR^r$)($OR^r$), -B(OH)$_2$, -B($OR^r$)$_2$ and S(O)$_2$NR^rR^r, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group

optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{6-10} aryl-C_{1-4} alkyl-, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NHR^i, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $NR^iC(=NOH)NR^iR^i$, $NR^iC(=NCN)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, $-P(O)R^iR^i$, $-P(O)(OR^i)(OR^i)$, $-B(OH)_2$, $-B(OR^i)_2$ and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, $-P(O)R^kR^k$, $-P(O)(OR^k)(OR^k)$, $-B(OH)_2$, $-B(OR^k)_2$ and $S(O)_2NR^kR^k$, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl, taken together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or any two R^k substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or any two R^o substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^{10} substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^{11} substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^q are each optionally substituted with halo, OH, CN, -COOH, NH_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments, the present disclosure provides a compound of Formula (I),

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aC(=NOH)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered

heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, ethyl, propyl, isopropyl, butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$,

$NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{5-6} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered

heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^c 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $NR^gC(=NOH)NR^gR^g$, $NR^gC(=NCN)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, $NR^oC(O)OR^o$, $C(=NR^o)NR^oR^o$, $NR^oC(=NR^o)NR^oR^o$, $S(O)R^o$, $S(O)NR^oR^o$, $S(O)_2R^o$, $NR^oS(O)_2R^o$, $NR^oS(O)_2NR^oR^o$, and $S(O)_2NR^oR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered

heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, $NR^rC(O)R^r$, $NR^rC(O)NR^rR^r$, $NR^rC(O)OR^r$, $C(=NR^r)NR^rR^r$, $NR^rC(=NR^r)NR^rR^r$, $NR^rC(=NOH)NR^rR^r$, $NR^rC(=NCN)NR^rR^r$, $S(O)R^r$, $S(O)NR^rR^r$, $S(O)_2R^r$, $NR^rS(O)_2R^r$, $NR^rS(O)_2NR^rR^r$ and $S(O)_2NR^rR^r$, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered

heteroaryl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{6-10} aryl-C_{1-4} alkyl-, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NHR^i, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $NR^iC(=NOH)NR^iR^i$, $NR^iC(=NCN)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$; wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl, taken together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^k substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^o substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^q are each optionally substituted with halo, OH, CN, -COOH, NH_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aC(=NOH)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered

heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, ethyl, propyl, isopropyl, butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4}

alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{5-6} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents.

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

cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $NR^gC(=NOH)NR^gR^g$, $NR^gC(=NCN)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, $NR^oC(O)OR^o$, $C(=NR^o)NR^oR^o$, $NR^oC(=NR^o)NR^oR^o$, $S(O)R^o$, $S(O)NR^oR^o$, $S(O)_2R^o$, $NR^oS(O)_2R^o$, $NR^oS(O)_2NR^oR^o$, and $S(O)_2NR^oR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

each R^e 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-

, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^e are each optionally substituted with 1, 2 or 3 independently selected R^f substituents;

each R^g 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, $NR^rC(O)R^r$, $NR^rC(O)NR^rR^r$, $NR^rC(O)OR^r$, $C(=NR^r)NR^rR^r$, $NR^rC(=NR^r)NR^rR^r$, $NR^rC(=NOH)NR^rR^r$, $NR^rC(=NCN)NR^rR^r$, $S(O)R^r$, $S(O)NR^rR^r$, $S(O)_2R^r$, $NR^rS(O)_2R^r$, $NR^rS(O)_2NR^rR^r$ and $S(O)_2NR^rR^r$, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{6-10} aryl-C_{1-4} alkyl-, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NHR^i, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $NR^iC(=NOH)NR^iR^i$, $NR^iC(=NCN)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each optionally substituted by 1, 2, or 3 R^j

substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$; wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl, taken together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^q substituents;

or any two R^k substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^q substituents;

or any two R^o substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^q are each optionally substituted with halo, OH, CN, -COOH, NH_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-10}

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

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aC(=NOH)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$,

$NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, ethyl, propyl, isopropyl, butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{5-6} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered

heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-}

$_{10}$ aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^c 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $NR^gC(=NOH)NR^gR^g$, $NR^gC(=NCN)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected

from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, $NR^oC(O)OR^o$, $C(=NR^o)NR^oR^o$, $NR^oC(=NR^o)NR^oR^o$, $S(O)R^o$, $S(O)NR^oR^o$, $S(O)_2R^o$, $NR^oS(O)_2R^o$, $NR^oS(O)_2NR^oR^o$, and $S(O)_2NR^oR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, $NR^rC(O)R^r$, $NR^rC(O)NR^rR^r$, $NR^rC(O)OR^r$, $C(=NR^r)NR^rR^r$, $NR^rC(=NR^r)NR^rR^r$, $NR^rC(=NOH)NR^rR^r$, $NR^rC(=NCN)NR^rR^r$, $S(O)R^r$, $S(O)NR^rR^r$, $S(O)_2R^r$, $NR^rS(O)_2R^r$, $NR^rS(O)_2NR^rR^r$ and $S(O)_2NR^rR^r$, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{6-10} aryl-C_{1-4} alkyl-, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NHR^i, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $NR^iC(=NOH)NR^iR^i$, $NR^iC(=NCN)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$; wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl, taken together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or any two R^k substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or any two R^o substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$, wherein the C_{1-6} alkyl,

phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^q are each optionally substituted with halo, OH, CN, -COOH, NH_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments, any two R^i substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or any two R^k substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q.

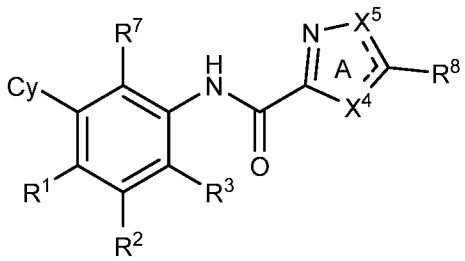
In some embodiments, R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents; and

R^9 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-

, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{b1} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

In some embodiments, the compound provided herein is a compound having Formula (II):



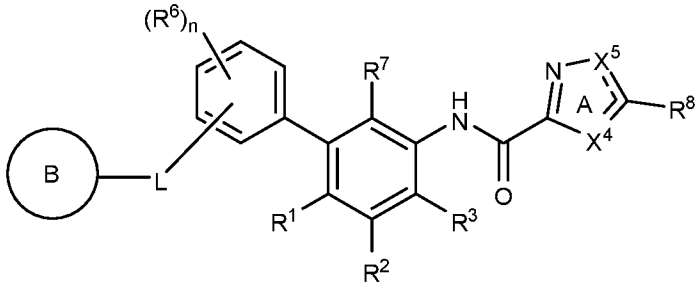
(II)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, (i) X^1 is N, X^2 is CR^2 and X^3 is CR^3; (ii) X^1 is CR^1, X^2 is N and X^3 is CR^3; (iii) X^1 is CR^1, X^2 is CR^2 and X^3 is N; (iv) X^1 is N, X^2 is CR^2 and X^3 is N; (v) X^1 is N, X^2 is N and X^3 is CR^3; or (vi) X^1 is CR^1, X^2 is N and X^3 is N.

In some embodiments, X^1 is N, X^2 is CR^2 and X^3 is CR^3. In some embodiments, X^1 is CR^1, X^2 is N and X^3 is CR^3. In some embodiments, X^1 is CR^1, X^2 is CR^2 and X^3 is N. In some embodiments, X^1 is N, X^2 is CR^2 and X^3 is N. In some embodiments, X^1 is N, X^2 is N and X^3 is CR^3. In some embodiments, X^1 is CR^1, X^2 is N and X^3 is N.

In some embodiments, the compound provided herein is a compound having Formula (III):



(III)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

L is a bond, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, O, $-(CR^{14}R^{15})_q-$, $-(CR^{14}R^{15})_q-O-$, $-O(CR^{14}R^{15})_q-$, $-NR^{13}-$, $-(CR^{14}R^{15})_q-NR^{13}-$, $-NR^{13}-(CR^{14}R^{15})_q-$, -CH=CH-, —C≡C—, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-NR^{13}SO_2NR^{13}-$, $-NR^{13}C(O)O-$, $-OC(O)NR^{13}$ or $-NR^{13}C(O)NR^{13}-$;

each R^{13} is independently H, C_{1-6} haloalkyl or C_{1-6} alkyl optionally substituted with a substituent selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, halo, OH, -COOH, NH_2, $-NHC_{1-4}$ alkyl and $-N(C_{1-4}$ alkyl$)_2$;

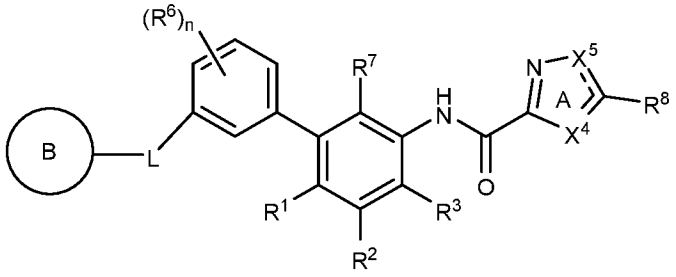
R^{14} and R^{15} are each independently selected from H, halo, CN, OH, -COOH, C_{1-4} alkyl, C_{1-4} alkoxy, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl$)_2$, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^{14} or R^{15} are each optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or R^{14} and R^{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R^q substituents;

ring B is C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2 or 3 independently selected R^d substituents; and

the subscript n is an integer of 1, 2, 3 or 4.

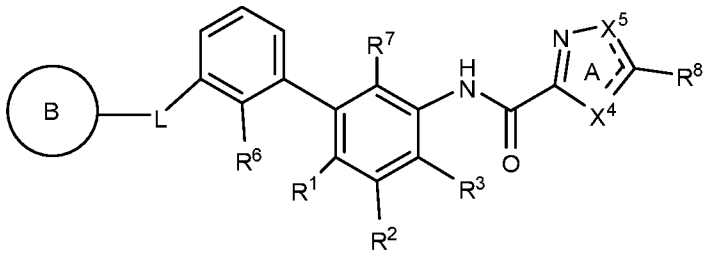
In some embodiments, the compound provided herein is a compound having Formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring B, L, R^6, n, R^1, R^2, R^3, R^7, X^4, X^5, and R^8 are as described herein.

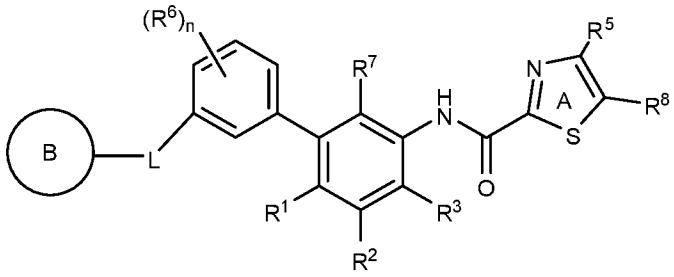
In some embodiments, the compound provided herein is a compound having Formula (IIIa-1):



(IIIa-1)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring B, L, R^6, R^1, R^2, R^3, R^7, X^4, X^5, and R^8 are as described herein

In some embodiments, the compound provided herein is a compound having Formula (IIIa-2):



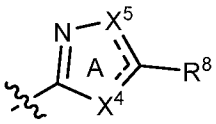
(IIIa-2)

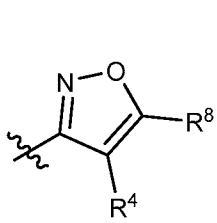
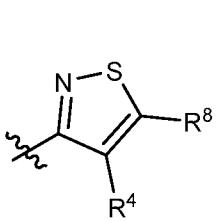
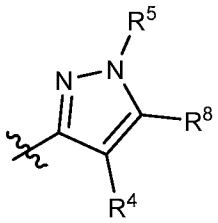
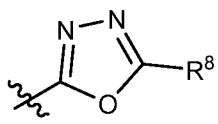
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring B, L, R^6, n, R^1, R^2, R^3, R^7, R^5, and R^8 are as described herein.

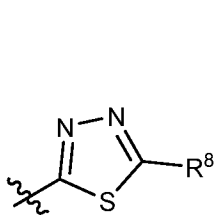
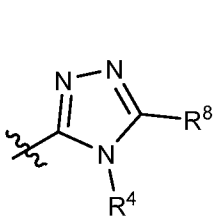
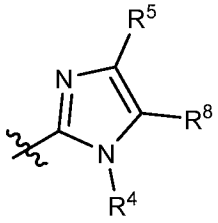
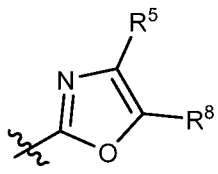
In some embodiments, R^d is C_{1-6} alkyl, phenyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, OR^e, $C(O)R^e$, halo or CN, wherein the C_{1-6} alkyl, phenyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4}

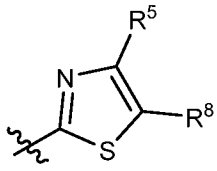
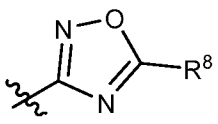
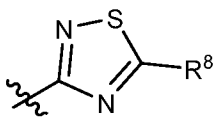
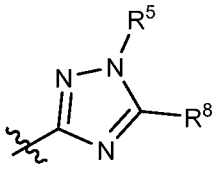
alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1, 2 or 3 independently selected R^f substituents.

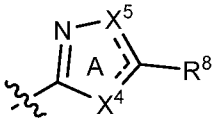
In some embodiments, R^d is (3-carboxypyrrolidin-1-yl)methyl, (R)-(3-carboxypyrrolidin-1-yl)methyl, (S)-(3-carboxypyrrolidin-1-yl)methyl, (3-hydroxypyrrolidin-1-yl)methyl, (R)-(3-hydroxypyrrolidin-1-yl)methyl, (S)-(3-hydroxypyrrolidin-1-yl)methyl, (2-hydroxyethylamino)methyl, (2-hydroxy-2-methylpropylamino)methyl, 2-(dimethylamino)ethanoyl, 2-(3-carboxyazetidin-1-yl)ethanoyl, (R)-2-(3-carboxyazetidin-1-yl)ethanoyl, (S)-2-(3-carboxyazetidin-1-yl)ethanoyl, 2-(2-carboxypiperidin-1-yl)ethanoyl, (R)-2-(2-carboxypiperidin-1-yl)ethanoyl, (S)-2-(2-carboxypiperidin-1-yl)ethanoyl, 2-(3-carboxypyrrolidin-1-yl)ethanoyl, (S)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (R)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (5-cyanopyridin-3-yl)methoxy, (2-hydroxyethylamino)methyl, 2-carboxy-1-piperidinylmethyl, (S)-2-carboxy-1-piperidinylmethyl, (R)-2-carboxy-1-piperidinylmethyl, halo or CN.

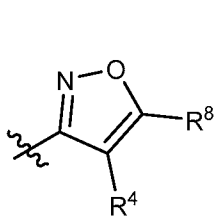
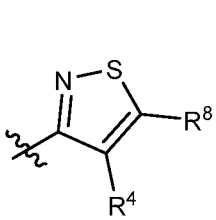
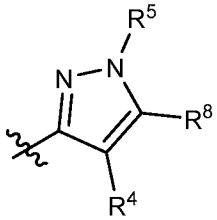
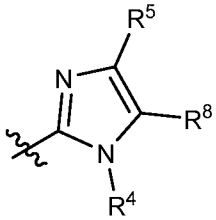
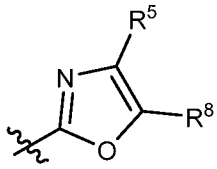
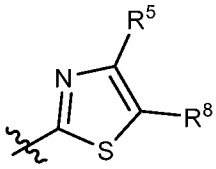
In some embodiments, the moiety  is selected from:

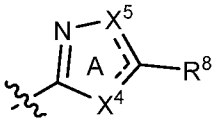
, , , ,

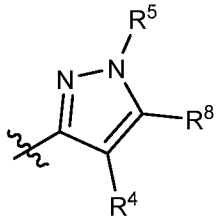
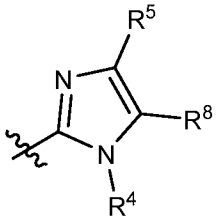
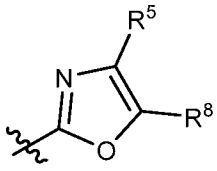
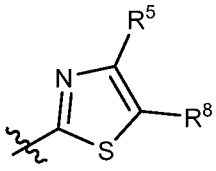
, , , ,

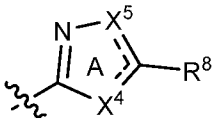
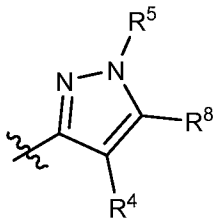
, , , and .

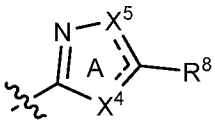
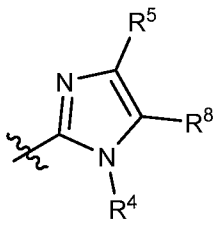
In some embodiments, the moiety  is selected from:

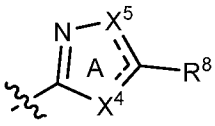
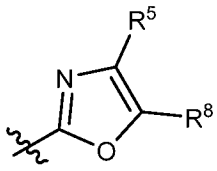





, and .

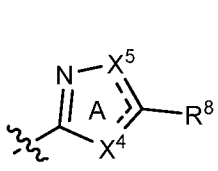
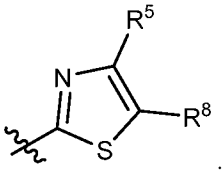
In some embodiments, the moiety  is selected from:




, and .

In some embodiments, the moiety  is .

In some embodiments, the moiety  is .

In some embodiments, the moiety  is .

In some embodiments, the moiety  is .

In some embodiments, (i) X^4 is S and X^5 is CR^5; (ii) X^4 is O and X^5 is CR^5; (iii) X^4 is NR^4 and X^5 is CR^5; or (iv) X^4 is CR^4 and X^5 is NR^5. In some embodiments, X^4 is S and X^5 is CR^5. In some embodiments, X^4 is O and X^5 is CR^5. In some embodiments, X^4 is NR^4 and X^5 is CR^5. In some embodiments, X^4 is CR^4 and X^5 is NR^5.

In some embodiments, Cy is phenyl, 5- or 6-membered heteroaryl, C_{3-6} cycloalkyl or 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents; or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents.

In some embodiments, Cy is phenyl, 2-thiophenyl, 3-thiophenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3,6-dihydro-2H-pyran-4-yl, cyclohexyl, cyclohexenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxin-5-yl, 2-methylindazol-6-yl or 1-methylindazol-4-yl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents.

In some embodiments, Cy is phenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-fluorophenyl, 2-fluoro-3-methoxyphenyl, or 1-methyl-1H-indazol-4-yl. For example, Cy is unsubstituted phenyl. In some embodiments, Cy is phenyl optionally substituted with 1 to 5 independently selected R^6 substituents. In certain embodiments, Cy is phenyl is substituted with 1 to 5 substituents selected from halo or OR^a. In certain embodiments, Cy is phenyl is substituted with 1 to 2 substituents selected from halo or O-C_{1-6} alkyl.

In some embodiments, R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NHR^{10}, -$NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$,

$C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 groups-independently selected from halo, OH, CN and C_{1-4} alkoxy.

In some embodiments, R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NH-C_{1-4} alkyl, and -N(C_{1-4} alkyl)$_2$.

In some embodiments, R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, and OH. For example, R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl. In certain embodiments, R^1, R^2 and R^3 are H.

In some embodiments, R^4 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl or C_{1-6} haloalkoxy. In some embodiments, R^4 is H.

In some embodiments, R^5 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl or C_{1-6} haloalkoxy. In some embodiments, R^5 is H.

In some embodiments, R^6 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, OR^a, $C(O)NR^aR^a$, or $NR^aC(O)R^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents; or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents.

In some embodiments, R^6 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, or OR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents; or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents.

In some embodiments, R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl or phenyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl and phenyl are each optionally substituted with 1, 2 or 3 independently selected R^q substituents.

In some embodiments, R^8 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- optionally substituted with 1, 2 or 3 independently selected R^b substituents. In some embodiments, R^8 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents.

In some embodiments, R^8 is C_{1-6} alkyl or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- are each optionally substituted with 1, 2 or 3 independently selected R^b substituents.

In some embodiments, R^8 is C_{1-6} alkyl substituted with R^b.

In some embodiments, R^8 is $–CH_2NHR^c$ or $–CH_2NR^cR^c$.

In some embodiments, R^8 is (2-hydroxyethylamino)methyl, 2-carboxy-1-piperidinylmethyl, (S)-2-carboxy-1-piperidinylmethyl, (R)-2-carboxy-1-piperidinylmethyl, or 3-hydroxypyrrolidin-1-ylmethyl.

In some embodiments, R^8 is (2-hydroxyethylamino)methyl, 2-carboxy-1-piperidinylmethyl, (S)-2-carboxy-1-piperidinylmethyl, or (R)-2-carboxy-1-piperidinylmethyl.

In some embodiments:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is phenyl, C_{3-6} cycloalkyl, 5- to 6-membered heteroaryl, or 4- to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused 5-, 6- or 7-membered heterocycloalkyl ring, or a fused 5- or 6-membered heteroaryl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, COOH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, cyclopropyl, cyclopropylmethyl, phenyl, phenyl-C_{1-4} alkyl-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkyl-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, NH_2, -NHC_{1-4} alkyl, -$N(C_{1-4}$ alkyl$)_2$, -$C(O)R^{10}$, -$O(CO)R^{10}$, -$C(O)OR^{10}$, -$O(CO)NHR^{10}$, -$NHC(O)OR^{10}$, -$NHC(O)NHR^{10}$, -$C(O)NHR^{10}$, -$NHC(O)R^{10}$, -SO_2R^{10}, -$NHSO_2R^{10}$ and -SO_2NHR^{10}, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, cyclopropyl, cyclopropylmethyl, phenyl, phenyl-C_{1-4} alkyl-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkyl-, 4-6 membered heterocycloalkyl and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2 or R^3 are each optionally substituted with halo, OH, CN or C_{1-4} alkoxy;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- or (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, COOH, NO_2, OR^a, $C(O)OR^a$, NH_2, -NHR^a, -$N(R^a)_2$, -$C(O)R^a$, -$O(CO)R^a$, -$C(O)OR^a$, -$O(CO)NR^aR^a$, -$NHC(O)OR^a$, -$NHC(O)NR^aR^a$, -$C(O)NR^aR^a$, -$NHC(O)R^a$, -SO_2R^a, -$NHSO_2R^a$ and -$SO_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered

heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1 or 2 R^b substituents;

R^7 is halo, C_{1-6} alkyl, CN, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- and (5-6 membered heteroaryl)-C_{1-4} alkyl of R^7 are each optionally substituted with 1 or 2 susbtituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy,CN, OH, NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, COOH, -OC_{1-6} alkyl, -SC_{1-6} alkyl, C(O)NH_2, -C(O)NH(C_{1-6} alkyl), -C(O)NH(C_{1-6} alkyl)$_2$, -C(O)OC_{1-6} alkyl, -OC(O)NHC_{1-6} alkyl, -OC(O)NH_2, -OC(O)NH(C_{1-6} alkyl)$_2$, -NHC(O)C_{1-6} alkyl, -NHC(O)H, -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -NHC(O)OC_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)OC_{1-6} alkyl, -NHC(O)NH(C_{1-6} alkyl), -NHC(O)N(C_{1-6} alkyl)$_2$, -NHC(O)NH_2, -N(C_{1-6} alkyl)C(O)NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)C(O)N(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)C(O)NH_2, -NHS(O)$_2$(C_{1-6} alkyl), -N(C_{1-6} alkyl)S(O)$_2$(C_{1-6} alkyl), -NHS(O)$_2NH_2$, -NHS(O)$_2$NH(C_{1-6} alkyl), -NHS(O)$_2$N(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)S(O)$_2NH_2$, -N(C_{1-6} alkyl)S(O)$_2$NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)S(O)$_2$N(C_{1-6} alkyl)$_2$, -S(O)$_2$(C_{1-6} alkyl), -S(O)$_2NH_2$, -S(O)$_2$NH(C_{1-6} alkyl) and -S(O)$_2$N(C_{1-6} alkyl)$_2$;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, OR^{11}, NH_2, -NHR^9, -NR^9R^{11}, C(O)R^{11}, C(O)$NR^{11}R^{11}$, C(O)OR^{11}, OC(O)$NR^{11}R^{11}$, NR^{11}C(O)R^{11}, NR^{11}C(O)OR^{11}, NR^{11}C(O)$NR^{11}R^{11}$, NR^{11}S(O)R^{11}, NR^{11}S(O)$_2R^{11}$, NR^{11}S(O)$_2NR^{11}R^{11}$, S(O)$_2R^{11}$, or S(O)$_2NR^{11}R^{11}$, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents; and

R^9 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- or (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} is independently selected from H, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1 or 2 R^b substituents;

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

each R^b is independently selected from halo, 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_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NHR^c, $N(R^c)_2$, OR^c, $C(O)NR^cR^c$, $C(O)OR^c$, COOH, $NR^cC(O)R^c$, $OC(O)NR^cR^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each optionally substituted with 1 or 2 R^d substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkyl-, CN, OH, COOH, OR^e, $C(O)OR^e$, NH_2, $-NHR^e$, $-N(R^e)_2$, $-C(O)NR^eR^e$, $-NR^eC(O)R^e$, $OC(O)NR^eR^e$, $NR^eC(O)OR^e$, $NR^eC(O)NR^eR^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, $S(O)_2R^e$ and $S(O)_2NR^eR^e$, wherein R^e is H or C_{1-6} alkyl;

each R^c is independently selected from H, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1 or 2 R^f substituents;

or two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1 or 2 independently selected R^h substituents;

each R^f is independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, CN, OH, COOH, OR^g, $C(O)OR^g$, NH_2, $-NHR^g$, $-N(R^g)_2$, $-C(O)NR^gR^g$, $-NR^gC(O)R^g$, $OC(O)NR^gR^g$, $NR^gC(O)OR^g$, $NR^gC(O)NR^gR^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, $S(O)_2R^g$ and $S(O)_2NR^gR^g$, wherein each R^g is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; and

each R^h is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, NHR^i, $N(R^i)_2$, OR^i, $C(O)NR^iR^i$, $NR^iC(O)R^i$ and $C(O)OR^i$, wherein R^i is H or C_{1-6} alkyl.

In some embodiments:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, and $NR^{10}C(O)OR^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl,

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

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, and $NR^aC(O)OR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, and $NR^{11}C(O)OR^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, or $NR^{11}C(O)OR^{11}$, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl, wherein the C_{5-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, and $OC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, and $NR^cC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, and $NR^cC(O)OR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy,

C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c 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, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, and $NR^gC(O)OR^g$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, and $NR^oC(O)OR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, and $NR^eC(O)OR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

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

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6

membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$ and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NH-C_{1-4} alkyl, -$N(C_{1-4}$ alkyl$)_2$, wherein the C_{1-4} alkyl and C_{1-4} alkoxy of R^1, R^2 and R^3 are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, NHR^a, and NR^aR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $NR^{11}C(O)R^{11}$, and $NR^{11}C(O)OR^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6}

haloalkoxy of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and phenyl substituted with 1-3 independently selected R^{b1} substituents, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, $NHOR^c$, OR^c, $C(O)R^c$, $C(O)NR^cR^c$, and $C(O)OR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, OR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, and $NR^cC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, and $NR^cC(O)OR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c 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 R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, NHR^g, NR^gR^g, and $NR^gC(O)R^g$; each R^d is independently selected from C_{1-6} alkyl,

C_{1-6} haloalkyl, halo, CN, NH_2, $NHOR^e$, OR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, and $NR^eC(O)OR^e$;

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

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

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, NH_2, -NH-C_{1-4} alkyl, and -N(C_{1-4} alkyl)$_2$;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and OR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or CN, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, and C_{2-6} alkenyl, wherein the C_{2-6} alkenyl of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo and C_{1-6} alkyl;

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, NHR^c, NR^cR^c, and $NR^cC(O)R^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c 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 R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OR^g, $C(O)R^g$, $C(O)NR^gR^g$, NHR^g, and NR^gR^g;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, NH_2, OR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, NHR^e, NR^eR^e, and $NR^eC(O)R^e$;

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

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

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, and

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

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, and $NR^aC(O)OR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, and $NR^{11}C(O)OR^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, or $NR^{11}C(O)OR^{11}$, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6}

haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl, wherein the C_{5-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, and $OC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, and $NR^cC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH,

NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, and $NR^cC(O)OR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c 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, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, and $NR^gC(O)OR^g$; wherein the 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, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, and $NR^oC(O)OR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, and $NR^eC(O)OR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

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

halo, CN, OR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, and $NR^rC(O)R^r$;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$ and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, wherein the C_{1-4} alkyl and C_{1-4} alkoxy of R^1, R^2 and R^3 are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, NHR^a, NR^aR^a, and $NR^aC(O)R^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused

phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $NR^{11}C(O)R^{11}$, and $NR^{11}C(O)OR^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, $NHOR^c$, OR^c, $C(O)R^c$, $C(O)NR^cR^c$, and $C(O)OR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, OR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, and $NR^cC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, and $NR^cC(O)OR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy,

C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, OR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, NHR^g, NR^gR^g, and $NR^gC(O)R^g$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, OR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, NHR^o, NR^oR^o, and $NR^oC(O)R^o$;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, and $NR^eC(O)OR^e$, wherein the C_{1-6} alkyl and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (5-10 membered heteroaryl)-C_{1-4} alkyl-; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (5-10 membered heteroaryl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^r, $C(O)R^r$, $C(O)NR^rR^r$, and $C(O)OR^r$;

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

$\overline{\text{-----}}$ is a single bond or a double bond to maintain ring A being aromatic.

In some embodiments:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, NH_2, -NH-C_{1-4} alkyl, and -N(C_{1-4} alkyl)$_2$;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^a, $C(O)NR^aR^a$, and $NR^aC(O)R^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or CN, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{2-6} alkenyl and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^a is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 5-10 membered heteroaryl of R^a are each optionally substituted with 1, 2 or 3 independently selected R^d substituents;

each R^b substituent is independently selected from halo, C_{1-6} alkyl, and OR^c;

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, NHR^c, NR^cR^c, and $NR^cC(O)R^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, OR^g, $C(O)R^g$, $C(O)NR^gR^g$, NHR^g, and NR^gR^g; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, halo, CN, OR^o, and $C(O)OR^o$;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, OR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, NHR^e, NR^eR^e, and $NR^eC(O)R^e$; wherein the C_{1-6} alkyl and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

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

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

-----is a single bond or a double bond to maintain ring A being aromatic.

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 (while the embodiments are intended to be combined as if written in multiply dependent form). 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. Thus, it is contemplated as features described as embodiments of the compounds of Formula (I) can be combined in any suitable combination.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl and C_6 alkyl.

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.

At various places in the present specification, variables defining divalent linking groups may be described. It is specifically intended that each 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 $-(CR'R'')_nNR-$ and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, *e.g.*, mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. It is to be understood that substitution at a given atom results in a chemically stable molecule. The phrase "optionally substituted" means unsubstituted or substituted. 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.

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_{1-4}, C_{1-6} and the like.

The term "alkyl" employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chained or branched. The term "C_{n-m} alkyl", refers to an alkyl group having n to m carbon atoms. An alkyl group formally corresponds to an alkane with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. 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. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl,

ethyl, *n*-propyl, isopropyl, *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.

The term "alkenyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term "C_{n-m} alkenyl" refers to an alkenyl group having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl and the like.

The term "alkynyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. The term "C_{n-m} alkynyl" refers to an alkynyl group 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.

The term "alkylene", employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkylene group to the remainder of the compound. The term "C_{n-m} alkylene" refers to an alkylene group having n to m carbon atoms. Examples of alkylene groups include, but are not limited to, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl and the like.

The term "alkoxy", employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group is as defined above. The term "C_{n-m} alkoxy" refers to an alkoxy group, the alkyl group of which has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), *t*-butoxy and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The term "amino" refers to a group of formula $-NH_2$.

The term "carbonyl", employed alone or in combination with other terms, refers to a -C(=O)- group, which also may be written as C(O).

The term "cyano" or "nitrile" refers to a group of formula –C≡N, which also may be written as -CN.

The terms "halo" or "halogen", used alone or in combination with other terms, refers to fluoro, chloro, bromo and iodo. In some embodiments, "halo" refers to a halogen atom selected from F, Cl, or Br. In some embodiments, halo groups are F.

The term "haloalkyl" as used herein refers to an alkyl group in which one or more of the hydrogen atoms has been replaced by a halogen atom. The term "C_{n-m} haloalkyl" refers to a C_{n-m} alkyl group having n to m carbon atoms and from at least one up to {2(n to m)+1} halogen atoms, which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5 and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

The term "haloalkoxy", employed alone or in combination with other terms, refers to a group of formula -O-haloalkyl, wherein the haloalkyl group is as defined above. The term "C_{n-m} haloalkoxy" refers to a haloalkoxy group, the haloalkyl group of which has n to m carbons. Example haloalkoxy groups include trifluoromethoxy and the like. In some embodiments, the haloalkoxy group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The term "oxo" refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to carbon, or attached to a heteroatom forming a sulfoxide or sulfone group, or an *N*-oxide group. In some embodiments, heterocyclic groups may be optionally substituted by 1 or 2 oxo (=O) substituents.

The term "sulfido" refers to a sulfur atom as a divalent substituent, forming a thiocarbonyl group (C=S) when attached to carbon.

The term "aromatic" refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (*i.e.*, having (4n + 2) delocalized π (pi) electrons where n is an integer).

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 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, indanyl, indenyl and the like. In some embodiments, aryl groups have from 6 to about 10 ring carbon atoms. In some embodiments aryl groups have 6 carbon atoms. In some embodiments aryl groups have 10 ring carbon

atoms. In some embodiments, the aryl group is phenyl. In some embodiments, the aryl group is naphthyl.

The term "heteroatom" used herein is meant to include boron, phosphorus, sulfur, oxygen and nitrogen.

The term "heteroaryl" or "heteroaromatic," employed alone or in combination with other terms, refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from boron, phosphorus, sulfur, oxygen and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl has 5-14 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-10 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. In other embodiments, the heteroaryl is an eight-membered, nine-membered or ten-membered fused bicyclic heteroaryl ring. Example heteroaryl groups include, but are not limited to, pyridintl (pyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furanyl, thiophenyl, quinolinyl, isoquinolinyl, naphthyridinyl (including 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3- and 2,6-naphthyridine), indolyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1,2-*b*]thiazolyl, purinyl, and the like.

A five-membered heteroaryl ring is a heteroaryl group having five ring atoms wherein one or more (*e.g.*, 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary five-membered ring heteroaryls include thienyl, furyl, 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 and 1,3,4-oxadiazolyl.

A six-membered heteroaryl ring is a heteroaryl group having six ring atoms wherein one or more (*e.g.*, 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "cycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic hydrocarbon ring system (monocyclic, bicyclic or polycyclic), including cyclized alkyl and alkenyl groups. The term "C_{n-m} cycloalkyl" refers to a cycloalkyl that has n to m ring member carbon atoms. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) groups and spirocycles. Cycloalkyl groups can have 3, 4, 5, 6 or 7 ring-forming carbons (C_{3-7}). In some embodiments, the cycloalkyl group has 3 to 6 ring members, 3 to 5 ring members, or 3 to 4 ring members. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl group is a C_{3-6} monocyclic cycloalkyl group. Ring-forming carbon atoms of a cycloalkyl group can be optionally oxidized to form an oxo or sulfido group. Cycloalkyl groups also include cycloalkylidenes. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. 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, *e.g.*, 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. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "heterocycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain one or more alkenylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from nitrogen, boron, sulfur, oxygen and phosphorus, and which has 4-10 ring members, 4-7 ring members, or 4-6 ring members. Included within the term "heterocycloalkyl" are monocyclic 4-, 5-, 6- and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can include mono- or bicyclic (*e.g.*, having two fused or bridged rings) ring systems. In some embodiments, the heterocycloalkyl group is a monocyclic group having 1, 2 or 3 heteroatoms independently selected from nitrogen, sulfur and oxygen. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally oxidized to form an oxo or sulfido group or other oxidized linkage (*e.g.*, C(O), S(O), C(S) or $S(O)_2$, *N*-oxide *etc.*) or a nitrogen atom can be quaternized. 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 heterocycloalkyl ring, *e.g.*, 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. Examples of heterocycloalkyl groups include azetidinyl, azepanyl, dihydrobenzofuranyl, dihydrofuranyl, dihydropyranyl, morpholino, 3-oxa-9-azaspiro[5.5]undecanyl, 1-oxa-8-azaspiro[4.5]decanyl, piperidinyl, piperazinyl, oxopiperazinyl, pyranyl, pyrrolidinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,4-tetrahydroquinolinyl, tropanyl, and thiomorpholino.

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 an azetidin-3-yl ring is attached at the 3-position.

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 invention 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 invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. One method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, *e.g.*, 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.

In some embodiments, the compounds of the invention have the (*R*)-configuration. In other embodiments, the compounds have the (*S*)-configuration. In compounds with more than one chiral centers, each of the chiral centers in the compound may be independently (*R*) or (*S*), unless otherwise indicated.

Compounds of the invention 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, *e.g.*, 1*H*- and 3*H*-imidazole, 1*H*-, 2*H*- and 4*H*- 1,2,4-triazole, 1*H*- and 2*H*- isoindole and 1*H*- and 2*H*-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention 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 of the present disclosure can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 deuterium atoms. Synthetic methods for including isotopes into organic compounds are known in the art.

The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers and isotopes of the structures depicted. The term is also meant to refer to compounds of the inventions, regardless of how they are prepared, e.g.,

synthetically, through biological process (e.g., metabolism or enzyme conversion), or a combination thereof.

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. When in the solid state, the compounds described herein and salts thereof may occur in various forms and may, *e.g.*, take the form of solvates, including hydrates. The compounds may be in any solid state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid state form of the compound.

In some embodiments, the compounds of the invention, 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, *e.g.*, a composition enriched in the compounds of the invention. 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 of the invention, or salt thereof.

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 expressions, "ambient temperature" and "room temperature," 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, *e.g.*, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. The term "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 invention include the non-toxic salts of the parent compound formed, *e.g.*, from non-toxic inorganic or organic acids. The

pharmaceutically acceptable salts of the present invention 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 (MeCN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge *et al.*, *J. Pharm. Sci.*, **1977**, *66*(1), 1-19 and in Stahl *et al.*, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (Wiley, 2002). In some embodiments, the compounds described herein include the N-oxide forms.

II. Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

The reactions for preparing compounds of the invention 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.

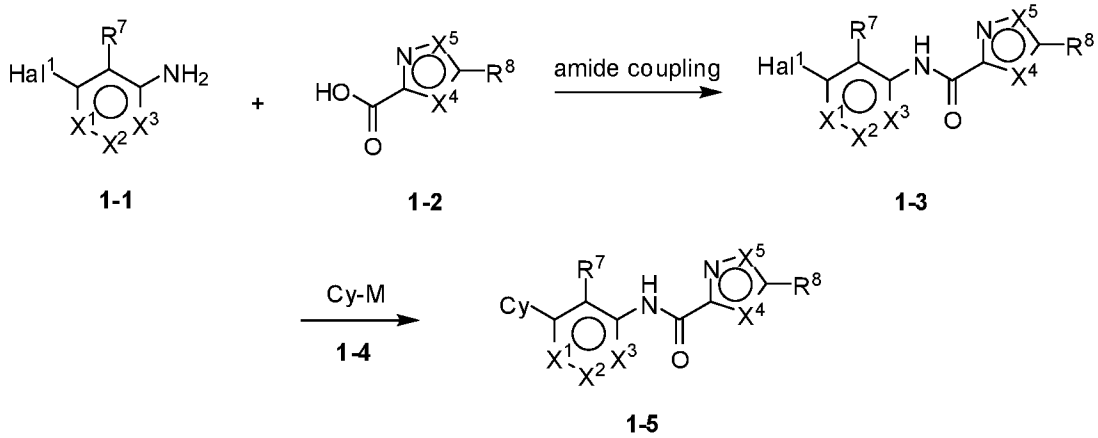
Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.*, in Kocienski, *Protecting Groups*, (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Peturssion *et al.*, "Protecting Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 1997, *74*(11), 1297; and Wuts *et al.*, *Protective Groups in Organic Synthesis*, 4th Ed., (Wiley, 2006).

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) or thin layer chromatography (TLC).

The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

Compounds of Formula (I) can be prepared, *e.g.*, using a process as illustrated in **Schemes 1-3**.

Scheme 1

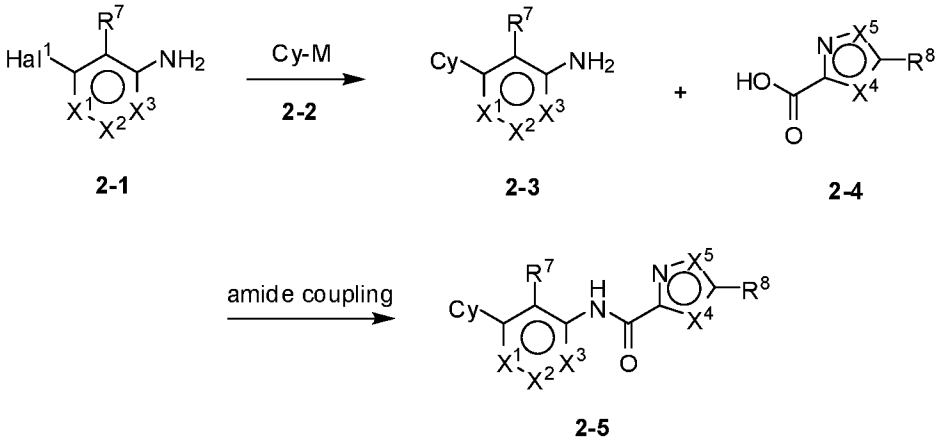


1-1 **1-2** **1-3** **1-4** **1-5**

Compounds of formula **1-5** can be prepared using procedures as outlined in **Scheme 1**. Acids of formula **1-2** can react with aromatic amines of formula **1-1** under amide coupling conditions [e.g., in the presence of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) and a suitable base such as N,N-diisopropylethylamine (DIPEA)] to give amide derivatives of formula **1-3**. The halide (e.g., Hal^1 = Cl, Br, I) in compounds **1-3** can be coupled to compounds of formula **1-4**, in which M is a boronic acid, boronic ester or an appropriately substituted metal [e.g., M is $B(OR)_2$, $Sn(Alkyl)_4$, or Zn-Hal], under Suzuki coupling conditions (e.g., in the presence of a palladium catalyst and a suitable base) or Stille coupling conditions (e.g., in the presence of a palladium catalyst), or Negishi coupling conditions (e.g., in the presence of a palladium catalyst) to give derivatives of formula **1-5**. Alternatively, compound **1-4** can be a cyclic amine (where M is H and attached to an amine nitrogen in ring Cy) and the coupling of aryl

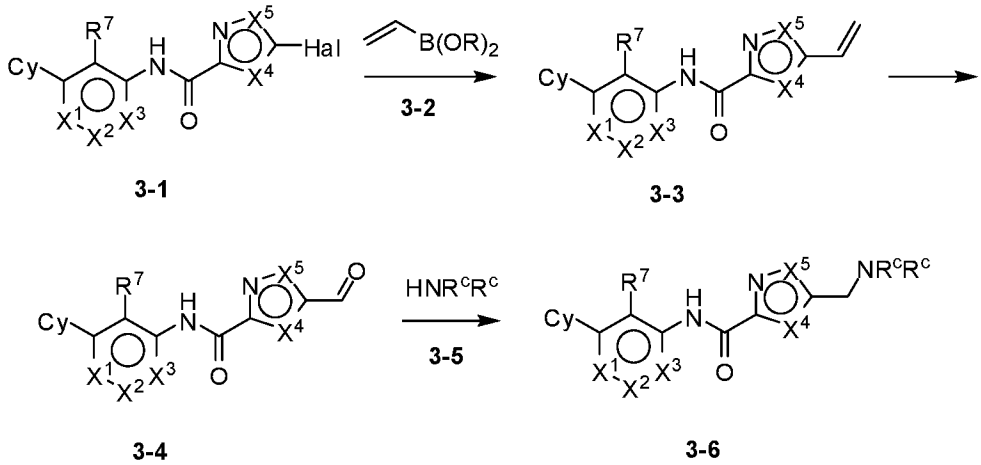
halide **1-3** with the cyclic amine **1-4** can be performed under Buchwald amination conditions (e.g., in the presence of a palladium catalyst and a base such as sodium tert-butoxide).

Scheme 2



Alternatively, compounds of formula **2-5** can also be prepared using reaction sequence as outlined in **Scheme 2**. Coupling of aromatic halides of formula **2-1** with compounds of formula **2-2** can be achieved using similar conditions as described in **Scheme 1** to give compounds of formula **2-3**. Acids of formula **2-4** can react with aromatic amines of formula **2-3** under amide coupling conditions to give compounds of formula **2-5**.

Scheme 3



Compounds of formula **3-6** can be prepared as outlined in **Scheme 3**, starting from compounds of formula **3-1** which can be prepared using synthetic routes as outlined in **Scheme 2** or **Scheme 1**. Coupling of heteroaryl halide **3-1** with vinyl boronic acid/ester **3-2** under Suzuki coupling conditions can give vinyl derivatives of formula **3-3**. Oxidative cleavage of the vinyl group in **3-3** (i.e., in the presence of $NaIO_4$ and OsO_4) can provide

aldehyde **3-4**. Reductive amination of aldehyde **3-4** with amine **3-5** can give the final compounds of formula **3-6**.

III. Uses of the Compounds

Compounds of the present disclosure can inhibit the activity of PD-1/PD-L1 protein/protein interaction and, thus, are useful in treating diseases and disorders associated with activity of PD-1 and the diseases and disorders associated with PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80). Advantageously, the compounds of the present disclosure demonstrate better efficacy and favorable safety and toxicity profiles in animal studies. In certain embodiments, the compounds of the present disclosure, or pharmaceutically acceptable salts or stereoisomers thereof, are useful for therapeutic administration to enhance, stimulate and/or increase immunity in cancer, sepsis, or chronic infection, including enhancement of response to vaccination. In some embodiments, the present disclosure provides a method for inhibiting or blocking the PD-1/PD-L1 protein/protein interaction. The method includes administering to an individual or a patient a compound of Formula (I) or any of the formulas as described herein or of a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof. The compounds of the present disclosure can be used alone, in combination with other agents or therapies or as an adjuvant or neoadjuvant for the treatment of diseases or disorders, including cancer or infection diseases. For the uses described herein, any of the compounds of the disclosure, including any of the embodiments thereof, may be used.

The compounds of the present disclosure inhibit the PD-1/PD-L1 protein/protein interaction, resulting in a PD-1 pathway blockade. The blockade of PD-1 can enhance the immune response to cancerous cells and infectious diseases in mammals, including humans. In some embodiments, the present disclosure provides treatment of an individual or a patient *in vivo* using a compound of Formula (I) or a salt or stereoisomer thereof such that growth of cancerous tumors is inhibited. A compound of Formula (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used to inhibit the growth of cancerous tumors. Alternatively, a compound of Formula (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used in conjunction with other agents or standard cancer treatments, as described below. In one embodiment, the present disclosure provides a method for inhibiting growth of tumor

cells *in vitro*. The method includes contacting the tumor cells *in vitro* with a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or of a salt or stereoisomer thereof. In another embodiment, the present disclosure provides a method for inhibiting growth of tumor cells in an individual or a patient. The method includes administering to the individual or patient in need thereof a therapeutically effective amount of a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or a salt or a stereoisomer thereof.

In some embodiments, provided herein is a method for treating cancer. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Examples of cancers include those whose growth may be inhibited using compounds of the disclosure and cancers typically responsive to immunotherapy.

In some embodiments, the present disclosure provides a method of enhancing, stimulating and/or increasing the immune response in a patient. The method includes administering to the patient in need thereof a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof.

Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, endometrial cancer, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T -cell lymphoma, environmentally

induced cancers including those induced by asbestos, and combinations of said cancers. The compounds of the present disclosure are also useful for the treatment of metastatic cancers, especially metastatic cancers that express PD-Ll.

In some embodiments, cancers treatable with compounds of the present disclosure include melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer, triple-negative breast cancer, colon cancer, lung cancer (e.g. non-small cell lung cancer and small cell lung cancer), squamous cell head and neck cancer, urothelial cancer (e.g. bladder) and cancers with high microsatellite instability (MSIhigh). Additionally, the disclosure includes refractory or recurrent malignancies whose growth may be inhibited using the compounds of the disclosure.

In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, solid tumors (*e.g.*, prostate cancer, colon cancer, esophageal cancer, endometrial cancer, ovarian cancer, uterine cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, sarcoma, bladder cancer, etc.), hematological cancers (*e.g.*, lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), DLBCL, mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma or multiple myeloma) and combinations of said cancers.

In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL) and multiple myeloma (MM).

Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, harmatoma, and teratoma.

Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer.

Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, meduoblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre -tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Exemplary skin cancers include melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids.In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to, sickle cell disease (e.g., sickle cell anemia), triple-negative breast cancer (TNBC), myelodysplastic syndromes, testicular cancer, bile duct cancer, esophageal cancer, and urothelial carcinoma.

PD-1 pathway blockade with compounds of the present disclosure can also be used for treating infections such as viral, bacteria, fungus and parasite infections. The present disclosure provides a method for treating infections such as viral infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, a salt thereof. Examples of viruses causing infections treatable by methods of the present disclosure include, but are not limit to, human immunodeficiency virus, human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus, poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome virus, ebola virus, and measles virus. In some embodiments, viruses causing infections treatable by methods of the present disclosure include, but are not limit to, hepatitis (A, B, or C), herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumpsvirus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

The present disclosure provides a method for treating bacterial infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of

pathogenic bacteria causing infections treatable by methods of the disclosure include chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

The present disclosure provides a method for treating fungus infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic fungi causing infections treatable by methods of the disclosure include Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

The present disclosure provides a method for treating parasite infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic parasites causing infections treatable by methods of the disclosure include Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

The terms "individual" or "patient," used interchangeably, refer to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent 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.

As used herein, the term "treating" or "treatment" refers to one or more of (1) inhibiting the disease; *e.g.*, 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); and

(2) ameliorating the disease; *e.g.*, 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.

Combination Therapies

Cancer cell growth and survival can be impacted by multiple signaling pathways. Thus, it is useful to combine different enzyme/protein/receptor inhibitors, exhibiting different preferences in the targets which they modulate the activities of, to treat such conditions. Targeting more than one signaling pathway (or more than one biological molecule involved in a given signaling pathway) may reduce the likelihood of drug-resistance arising in a cell population, and/or reduce the toxicity of treatment.

The compounds of the present disclosure can be used in combination with one or more other enzyme/protein/receptor inhibitors for the treatment of diseases, such as cancer or infections. Examples of cancers include solid tumors and liquid tumors, such as blood cancers. Examples of infections include viral infections, bacterial infections, fungus infections or parasite infections. For example, the compounds of the present disclosure can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, TGF-βR, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IGF-1R, IR-R, PDGFαR, PDGFβR, PI3K (alpha, beta, gamma, delta), CSFIR, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, Ron, Sea, TRKA, TRKB, TRKC, TAM kinases (Axl, Mer, Tyro3), FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. In some embodiments, the compounds of the present disclosure can be combined with one or more of the following inhibitors for the treatment of cancer or infections. Non-limiting examples of inhibitors that can be combined with the compounds of the present disclosure for treatment of cancer and infections include an FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, e.g.,

INCB54828, INCB62079 and INCB63904), a JAK inhibitor (JAK1 and/or JAK2, e.g., ruxolitinib, baricitinib or INCB39110), an IDO inhibitor (e.g., epacadostat, NLG919, and BMS-986205), an LSD1 inhibitor (e.g., INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor (e.g., INCB50797 and INCB50465), a PI3K-gamma inhibitor such as a PI3K-gamma selective inhibitor, a Pim inhibitor (e.g., INCB53914), a CSF1R inhibitor, a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer), an adenosine receptor antagonist (e.g., A2a/A2b receptor antagonist), an HPK1 inhibitor, an angiogenesis inhibitor, an interleukin receptor inhibitor, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors such as INCB54329 and INCB57643), an arginase inhibitor (INCB01158), and an adenosine receptor antagonist or combinations thereof.

Compounds of the present disclosure can be used in combination with one or more 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, TIM3, 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, GITR 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 anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

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 nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, 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 PD-1 antibody is SHR-1210.

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 or tremelimumab.

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, INCAGN2385 or LAG525.

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, INCAGN1876, MK-1248, AMG228, BMS-986156, GWN323, MEDI1873 or MK-4166.

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 OX40, e.g., an anti-OX40 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.

Compounds of the present disclosure 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).

The compounds of the present disclosure can further be used in combination with other methods of treating cancers, for example by chemotherapy, irradiation therapy, tumor-targeted therapy, adjuvant therapy, immunotherapy or surgery. Examples of immunotherapy include cytokine treatment (e.g., interferons, GM-CSF, G-CSF, IL-2), CRS-207 immunotherapy, cancer vaccine, monoclonal antibody, adoptive T cell transfer, Toll receptor agonists, STING agonists, oncolytic virotherapy and immunomodulating small molecules, including thalidomide or JAK1/2 inhibitor and the like. The compounds can be administered in combination with one or more anti-cancer drugs, such as a chemotherapeutics. Example

chemotherapeutics include any of: abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bevacizumab, bexarotene, baricitinib, bleomycin, bortezombi, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, meclorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelarabine, nofetumomab, oxaliplatin, paclitaxel, pamidronate, panitumumab, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat and zoledronate.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4 (e.g., ipilimumab), 4-1BB (e.g. urelumab, utomilumab), antibodies to PD-1 and PD-L1, or antibodies to cytokines (IL-10, TGF-β, etc.). Examples of antibodies to PD-1 and/or PD-L1 that can be combined with compounds of the present disclosure for the treatment of cancer or infections such as viral, bacteria, fungus and parasite infections include, but are not limited to, nivolumab, pembrolizumab, MPDL3280A, MEDI-4736 and SHR-1210.

The compounds of the present disclosure can further be used in combination with one or more anti-inflammatory agents, steroids, immunosuppressants or therapeutic antibodies.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with another immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. 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 Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to express GM-CSF. 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). In some embodiments, the compounds of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated from tumor tissue itself. In some embodiments, the compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with dendritic cells immunization to activate potent anti-tumor responses.

The compounds of the present disclosure can be used in combination with bispecific macrocyclic peptides that target Fe alpha or Fe gamma receptor-expressing effectors cells to tumor cells. The compounds of the present disclosure can also be combined with macrocyclic peptides that activate host immune responsiveness.

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.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self antigens. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to, HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa.

Viruses causing infections treatable by methods of the present disclosure include, but are not limit to human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus, poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome virus, ebola virus, measles virus, herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus,

respiratory syncytial virus, mumpsvirus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

Pathogenic bacteria causing infections treatable by methods of the disclosure include, but are not limited to, chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

Pathogenic fungi causing infections treatable by methods of the disclosure include, but are not limited to, Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

Pathogenic parasites causing infections treatable by methods of the disclosure include, but are not limited to, Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

When more than one pharmaceutical agent is administered to a patient, they can be administered simultaneously, separately, sequentially, or in combination (*e.g.*, for more than two agents).

IV. Formulation, Dosage Forms and Administration

When employed as pharmaceuticals, the compounds of the present disclosure can be administered in the form of pharmaceutical compositions. Thus the present disclosure provides a composition comprising a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt thereof, or any of the embodiments thereof, and at least one pharmaceutically acceptable carrier or excipient. 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 indicated 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, *e.g.*, 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 invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the present disclosure or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, *e.g.*, 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, *e.g.*, 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 invention 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 invention can be prepared by processes known in the art see, *e.g.*, 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 invention 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.

In some embodiments, the pharmaceutical composition comprises silicified microcrystalline cellulose (SMCC) and at least one compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the silicified microcrystalline cellulose comprises about 98% microcrystalline cellulose and about 2% silicon dioxide w/w.

In some embodiments, the composition is a sustained release composition comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose and polyethylene oxide. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and polyethylene oxide. In some embodiments, the composition further comprises magnesium stearate or silicon dioxide. In some embodiments, the microcrystalline cellulose is Avicel PH102™. In some embodiments, the lactose monohydrate is Fast-flo 316™. In some embodiments, the hydroxypropyl methylcellulose is hydroxypropyl methylcellulose 2208 K4M (*e.g.*, Methocel K4 M Premier™) and/or hydroxypropyl methylcellulose 2208 K100LV (*e.g.*, Methocel K00LV™). In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (*e.g.*, Polyox WSR 1105™).

In some embodiments, a wet granulation process is used to produce the composition. In some embodiments, a dry granulation process is used to produce the composition.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. In some embodiments, each dosage contains about 10 mg of the active

ingredient. In some embodiments, each dosage contains about 50 mg of the active ingredient. In some embodiments, each dosage contains about 25 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.

The components used to formulate the pharmaceutical compositions are of high purity and are substantially free of potentially harmful contaminants (*e.g.*, at least National Food grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Particularly for human consumption, the composition is preferably manufactured or formulated under Good Manufacturing Practice standards as defined in the applicable regulations of the U.S. Food and Drug Administration. For example, suitable formulations may be sterile and/or substantially isotonic and/or in full compliance with all Good Manufacturing Practice regulations of the U.S. Food and Drug Administration.

The active compound may be effective over a wide dosage range and is generally administered in a therapeutically 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.

The therapeutic dosage of a compound of the present invention can vary according to, *e.g.*, 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 invention 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 invention 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.

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 invention. 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, *e.g.*, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention 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 invention 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, *e.g.*, 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, *e.g.*, 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 invention. The topical formulations can be suitably packaged in tubes of, *e.g.*, 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 invention can vary according to, *e.g.*, 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 invention 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 invention 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.

V. Labeled Compounds and Assay Methods

The compounds of the present disclosure can further be useful in investigations of biological processes in normal and abnormal tissues. Thus, another aspect of the present invention relates to labeled compounds of the invention (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 PD-1 or PD-L1 protein in tissue samples, including human, and for identifying PD-L1 ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes PD-1/PD-L1 binding assays that contain such labeled compounds.

The present invention further includes isotopically-substituted compounds of the disclosure. An "isotopically-substituted" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having the same atomic number but different atomic mass or mass number e.g., a different atomic mass or mass number from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). It is to be understood that a "radio-labeled" is a compound that has incorporated at least one one isotope that is radioactive (e.g., radionuclide). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{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. 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* PD-L1 protein labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I, ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most 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. Synthetic methods for incorporating radio-isotopes into organic compounds are known in the art.

A radio-labeled compound of the invention can be used in a screening assay to identify and/or 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 a PD-L1 protein by monitoring its concentration variation when contacting with the PD-L1 protein, through tracking of the labeling. For example, a test compound (radio-labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to a PD-L1 protein (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the PD-L1 protein 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.

VI. Kits

The present disclosure also includes pharmaceutical kits useful, *e.g.*, in the treatment or prevention of diseases or disorders associated with the activity of PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80), such as cancer or infections, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, *e.g.*, 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.

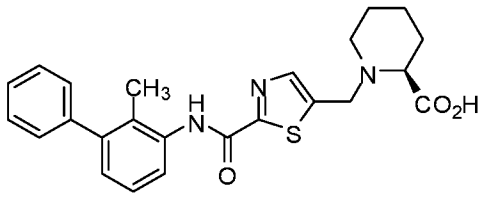
The compounds of the Examples have been found to inhibit the activity of PD-1/PD-L1 protein/protein interaction according to at least one assay described herein.

EXAMPLES

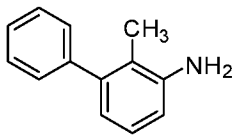
Experimental procedures for compounds of the invention are provided below. Open Access Preparative LCMS Purification of some of the compounds prepared was performed on Waters mass directed fractionation systems. The basic equipment setup, protocols and control software for the operation of these systems have been described in detail in literature. *See*, *e.g.*, Blom, "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Combi. Chem.*, **2002**, *4*, 295-301; Blom *et al.*, "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", *J. Combi. Chem.*, **2003**, *5*, 670-83; and Blom *et al.*, "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", *J. Combi. Chem.*, **2004**, *6*, 874-883.

Example 1

(2S)-1-[(2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1,3-thiazol-5-yl)methyl]piperidine-2-carboxylic acid

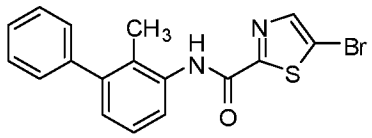


Step 1: 2-methylbiphenyl-3-amine



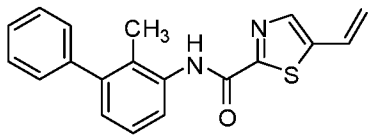
To a solution of 3-bromo-2-methylaniline (1.0 g, 5.4 mmol) in water (2.9 mL) and 1,4-dioxane (10 mL) were added phenylboronic acid (0.79 g, 6.4 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.3 g, 0.3 mmol) and sodium carbonate (1.2 g, 11 mmol). The resulting mixture was purged with nitrogen then stirred at 100 °C for 3 h. The reaction mixture was cooled to room temperature then filtered and concentrated to dryness. The residue was purified by silica gel chromatography eluting with 20% ethyl acetate in hexanes to give the desired product. LC-MS calculated for $C_{13}H_{14}N$ $(M+H)^+$: m/z = 184.1; found 184.1.

Step 2: 5-bromo-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide



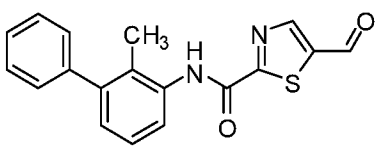
To a solution of 5-bromo-1,3-thiazole-2-carboxylic acid (AstaTech, cat#450324: 90 mg, 0.43 mmol) and 2-methylbiphenyl-3-amine (87 mg, 0.48 mmol) in N,N-dimethylformamide (5 mL) was added N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (250 mg, 0.65 mmol), followed by N,N-diisopropylethylamine (230 µL, 1.3 mmol). The resulting mixture was stirred at room temperature for 3 h then diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{17}H_{14}BrN_2OS$ $(M+H)^+$: m/z = 373.0; found 373.0.

Step 3: N-(2-methylbiphenyl-3-yl)-5-vinyl-1,3-thiazole-2-carboxamide



A mixture of 5-bromo-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide (crude product from Step 2: 160 mg, 0.43 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (110 µL, 0.64 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (20 mg, 0.02 mmol) and sodium carbonate (95 mg, 0.90 mmol) in 1,4-dioxane (4.7 mL) and water (800 µL) was purged with nitrogen and then stirred at 100 °C for 2 hours. The reaction mixture was cooled to room temperature then filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 15% AcOEt in hexanes to give the desired product (115 mg, 84 %). LC-MS calculated for $C_{19}H_{17}N_2OS$ $(M+H)^+$: m/z = 321.1; found 321.1.

Step 4: 5-formyl-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide



To a solution of N-(2-methylbiphenyl-3-yl)-5-vinyl-1,3-thiazole-2-carboxamide (115 mg, 0.359 mmol) in 1,4-dioxane (3.6 mL) was added 2,6-lutidine (170 µL, 1.4

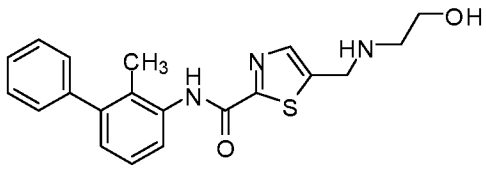
mmol), followed osmium tetraoxide (4 wt.% in water, 340 μL, 0.054 mmol) at room temperature. The mixture was stirred for 10 min then sodium periodate (230 mg, 1.1 mmol) in water (1.5 mL) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and then extracted with DCM. The combined extracts were washed with water and brine and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 20% AcOEt in hexanes to give the desired product. LC-MS calculated for $C_{18}H_{15}N_2O_2S$ $(M+H)^+$: m/z = 323.1; found 323.1.

Step 5: (2S)-1-[(2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1,3-thiazol-5-yl)methyl]piperidine-2-carboxylic acid

To a solution of 5-formyl-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide (20 mg, 0.062 mmol) in 1,2-Dichloroethane (1 mL) was added (2S)-piperidine-2-carboxylic acid (TCI, cat#P1404: 16 mg, 0.12 mmol). The mixture was stirred at room temperature for 20 min, then sodium triacetoxyborohydride (39 mg, 0.19 mmol) was added. The reaction mixture was stirred at room temperature overnight then concentrated. The residue was dissolved in MeOH and purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{24}H_{26}N_3O_3S$ $(M+H)^+$: m/z = 436.2; found 436.2.

Example 2

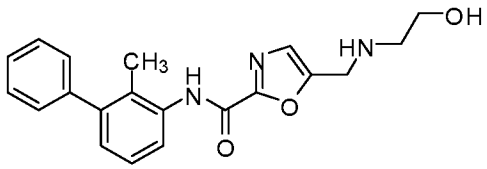
5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide



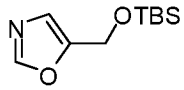
To a solution of 5-formyl-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide (Example 1, Step 4: 12.0 mg, 0.0372 mmol) in 1,2-dichloroethane (0.8 mL) was added ethanolamine (4.5 μL, 0.074 mmol). The resulting mixture was stirred at room temperature for 20 min, then sodium triacetoxyborohydride (24 mg, 0.11 mmol) was added. The mixture was stirred at room temperature overnight and then concentrated. The residue was dissolved in MeOH then purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{20}H_{22}N_3O_2S$ $(M+H)^+$: m/z = 368.1; found 368.1.

Example 3

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide

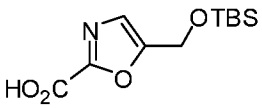


Step 1: 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-oxazole



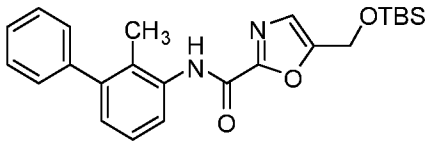
To a solution of 1,3-oxazol-5-ylmethanol (Ark Pharm, cat#AK-25343: 1.0 g, 10. mmol) in methylene chloride (10 mL) were added triethylamine (1.68 mL, 12.0 mmol) and 4-dimethylaminopyridine (65.2 mg, 0.534 mmol), followed by tert-butyldimethylsilyl chloride (1.59 g, 10.6 mmol) at room temperature. The mixture was stirred at room temperature overnight then diluted with water and extracted with DCM. The combined extracts were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 18% AcOEt in hexanes to give the desired product. LC-MS calculated for $C_{10}H_{20}NO_2Si$ $(M+H)^+$: m/z = 214.1; found 214.1.

Step 2: 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-oxazole-2-carboxylic acid



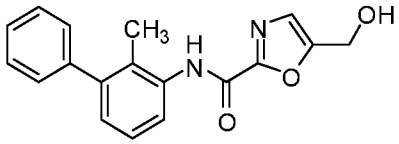
To a solution of 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-oxazole (0.75 g, 3.5 mmol) in tetrahydrofuran (30 mL) was added 2.5 M n-butyllithium in hexane (2.25 mL, 5.62 mmol) at -78 °C dropwise. The resulting mixture was stirred at -78 °C for 1 h then dry ice was added. The reaction mixture was slowly warmed to room temperature and stirred at room temperature overnight then quenched with water. The mixture was extracted with DCM/iPrOH. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 10 to 20 % MeOH in DCM to give the desired product. LC-MS calculated for $C_{11}H_{20}NO_4Si$ $(M+H)^+$: m/z = 258.1; found 258.1.

Step 3: 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide



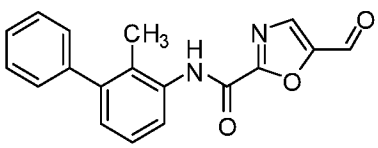
To a solution of 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-oxazole-2-carboxylic acid (42 mg, 0.16 mmol) and 2-methylbiphenyl-3-amine (Example 1, Step 1: 35 mg, 0.19 mmol) in N,N-dimethylformamide (2 mL) was added N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (93 mg, 0.24 mmol), followed by N,N-diisopropylethylamine (85 µL, 0.49 mmol). The resulting mixture was stirred at room temperature for 3 h. The reaction was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{24}H_{31}N_2O_3Si$ $(M+H)^+$: m/z = 423.2; found 423.1.

Step 4: 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide



To a solution of 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide (180 mg, 0.42 mmol) in tetrahydrofuran (2 mL) was added tetra-n-butylammonium fluoride (1M in THF, 0.85 mL, 0.85 mmol). The mixture was stirred at room temperature for 3 h and then diluted with EtOAc, washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 50% AcOEt in Hexanes to give the desired product. LC-MS calculated for $C_{18}H_{17}N_2O_3$ $(M+H)^+$: m/z = 309.1; found 309.2. ^1H NMR (600 MHz, DMSO) δ 10.37 (s, 1H), 7.49 – 7.44 (m, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.28 (m, 4H), 7.17 – 7.14 (m, 1H), 5.61 (s, 1H), 4.58 (s, 2H), 2.10 (s, 3H).

Step 5: 5-formyl-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide



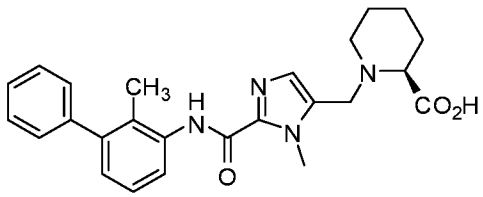
Dimethyl sulfoxide (40 μL, 0.56 mmol) was added to a solution of oxalyl chloride (2M in DCM, 0.14 mL, 0.28 mmol) in methylene chloride (0.6 mL) at -78 °C then a solution of 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide (43 mg, 0.14 mmol) in methylene chloride (0.2 mL) was slowly added. The mixture was stirred at -78 °C for 30 min and then N,N-diisopropylethylamine (0.19 mL, 1.1 mmol) was added. The reaction mixture was warmed slowly to 0 °C, which was then quenched with saturated $NaHCO_3$ aqueous solution and extracted with DCM. The combined extracts were washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{18}H_{15}N_2O_3$ $(M+H)^+$: m/z = 307.1; found 307.1.

Step 6: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide

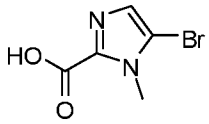
To a solution of 5-formyl-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide (11.4 mg, 0.0372 mmol) in methylene chloride (1 mL) was added ethanolamine (4.5 μL, 0.074 mmol). The mixture was stirred at room temperature for 20 min, then sodium triacetoxyborohydride (24 mg, 0.11 mmol) was added. The reaction mixture was stirred at room temperature overnight and then NaBH4 (10 mg) and MeOH (0.2 mL) were added. The mixture was stirred for another 2 h at room temperature, which was then concentrated. The residue was dissolved in MeOH then purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{20}H_{22}N_3O_3$ $(M+H)^+$: m/z = 352.2; found 352.2.

Example 4

(2S)-1-[(1-methyl-2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1H-imidazol-5-yl)methyl]piperidine-2-carboxylic acid



Step 1: 5-bromo-1-methyl-1H-imidazole-2-carboxylic acid



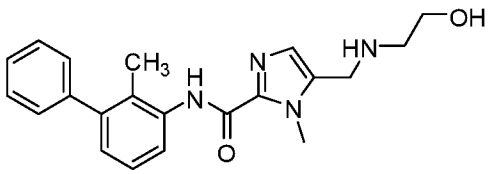
To a mixture of ethyl 5-bromo-1-methyl-1H-imidazole-2-carboxylate (Anichem, cat#K20110: 250 mg, 1.1 mmol) in tetrahydrofuran (20 mL) were added lithium hydroxide monohydrate (230 mg, 5.6 mmol) and water (0.4 mL). The resulting mixture was stirred at room temperature for 2 h then concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_5H_6BrN_2O_2$ $(M+H)^+$: m/z = 205.0; found 205.0.

Step 2: (2S)-1-[(1-methyl-2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1H-imidazol-5-yl)methyl]piperidine-2-carboxylic acid

This compound was prepared using similar procedures as described for Example 1 with 5-bromo-1-methyl-1H-imidazole-2-carboxylic acid (Step 1) replacing 5-bromo-1,3-thiazole-2-carboxylic acid in Step 2. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{25}H_{29}N_4O_3$ $(M+H)^+$: m/z = 433.2; found 433.2.

Example 5

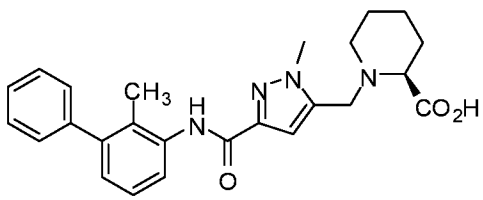
5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-N-(2-methylbiphenyl-3-yl)-1H-imidazole-2-carboxamide



This compound was prepared using similar procedures as described for Example 4 with ethanolamine replacing (2S)-piperidine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{21}H_{25}N_4O_2$ $(M+H)^+$: m/z = 365.2; found 365.2.

Example 6

(2S)-1-[(1-methyl-3-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1H-pyrazol-5-yl)methyl]piperidine-2-carboxylic acid

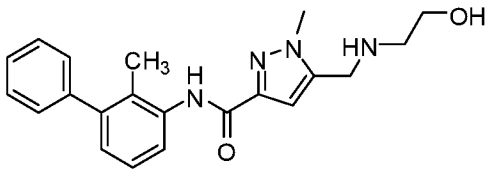


This compound was prepared using similar procedures as described for Example 1

with 5-bromo-1-methyl-1H-pyrazole-3-carboxylic acid (AstaTech, cat#80200) replacing 5-bromo-1,3-thiazole-2-carboxylic acid in Step 2. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{25}H_{29}N_4O_3$ $(M+H)^+$: m/z = 433.2; found 433.2.

Example 7

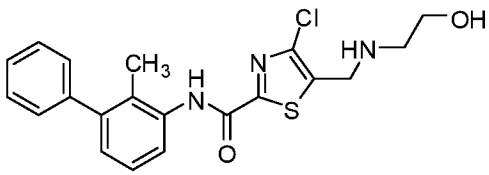
5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-N-(2-methylbiphenyl-3-yl)-1H-pyrazole-3-carboxamide



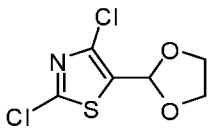
This compound was prepared using similar procedures as described for Example 6 with ethanolamine replacing (2S)-piperidine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{25}N_4O_2$ $(M+H)^+$: m/z = 365.2; found 365.2.

Example 8

4-chloro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide



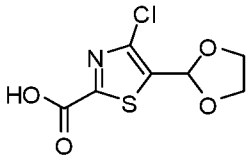
Step 1: 2,4-dichloro-5-(1,3-dioxolan-2-yl)-1,3-thiazole



2,4-Dichloro-1,3-thiazole-5-carbaldehyde (*Combi-Blocks, cat#HI-1210*: 3.5 g, 19 mmol) and p-toluenesulfonic acid monohydrate (180 mg, 0.96 mmol) were dissolved in toluene (40 mL) and then 1,2-ethanediol (3.2 mL, 58 mmol) was added. The mixture was heated to reflux for overnight with azotropic removal of water via Dean Stark trap. The solution was cooled to room temperature and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was

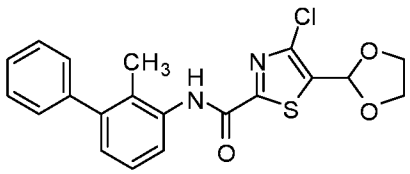
purified by flash chromatography eluting with 15% EtOAc/Hexanes to give the desired product (3.9 g, 90 %). LC-MS calculated for $C_6H_6Cl_2NO_2S$ $(M+H)^+$: m/z = 225.9; found 226.0.

Step 2: 4-chloro-5-(1,3-dioxolan-2-yl)-1,3-thiazole-2-carboxylic acid



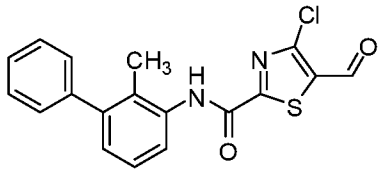
To a solution of 2,4-dichloro-5-(1,3-dioxolan-2-yl)-1,3-thiazole (3.9 g, 17 mmol) in tetrahydrofuran (60 mL) was added 2.5 M n-butyllithium in hexanes (7.24 mL, 18.1 mmol) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 30 min then CO_2 gas (generated from dry ice) was bubbled through the mixture for 10 min. The reaction mixture was slowly warmed to room temperature and stirred overnight, then concentrated to dryness. The residue was titurated with cold EtOAc then filtered and dried to give the desired product (4.0 g, 98 %), which was used in the next step without further purification. LC-MS calculated for $C_7H_7ClNO_4S$ $(M+H)^+$: m/z = 236.0; found 235.9.

Step 3: 4-chloro-5-(1,3-dioxolan-2-yl)-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide



To a solution of 4-chloro-5-(1,3-dioxolan-2-yl)-1,3-thiazole-2-carboxylic acid (400.0 mg, 1.697 mmol) and 2-methylbiphenyl-3-amine (*Example 1, Step 1*: 360 mg, 2.0 mmol) in N,N-dimethylformamide (20 mL) was added N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (970 mg, 2.5 mmol), followed by N,N-diisopropylethylamine (890 µL, 5.1 mmol). The mixture was stirred at room temperature for 3 h and then diluted with EtOAc, washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 25% AcOEt in Hexanes to give the desired product (0.65 g, 96 %). LC-MS calculated for $C_{20}H_{18}ClN_2O_3S$ $(M+H)^+$: m/z = 401.1; found 401.1.

Step 4: 4-chloro-5-formyl-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide



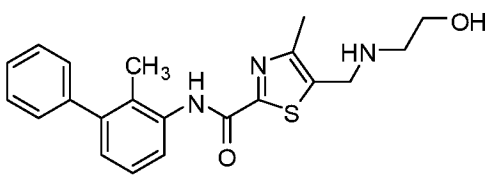
To a solution of 4-chloro-5-(1,3-dioxolan-2-yl)-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide (650 mg, 1.6 mmol) in tetrahydrofuran (3 mL) was added 2.0 M hydrogen chloride in water (8.1 mL, 16 mmol). The resulting mixture was stirred at 50 °C overnight then cooled to room temperature and concentrated. The residue was dissolved in EtOAc then washed with saturated $NaHCO_3$ aqueous solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{18}H_{14}ClN_2O_2S$ $(M+H)^+$: m/z = 357.0; found 357.0.

Step 5: 4-chloro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide

To a solution of 4-chloro-5-formyl-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide (200. mg, 0.560 mmol) in methylene chloride (20 mL) was added ethanolamine (68 µL, 1.1 mmol). The mixture was stirred at room temperature for 20 min, then sodium triacetoxyborohydride (360 mg, 1.7 mmol) was added. The reaction mixture was stirred at room temperature overnight. LC-MS indicated that some of the imine-intermediate was not reduced, so a small amount $NaBH_4$ (30 mg) and MeOH (1 mL) were added. The mixture was stirred for another 2 h at room temperature then concentrate. The residue was dissolved in DCM, then washed with $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 5 % MeOH in DCM to give the desired product (105 mg, 47 %). LC-MS calculated for $C_{20}H_{21}ClN_3O_2S$ $(M+H)^+$: m/z = 402.1; found 402.1.

Example 9

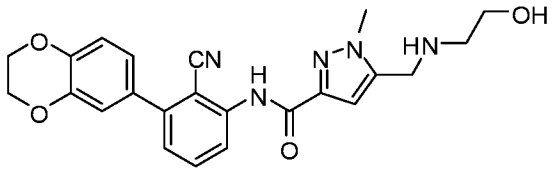
5-{[(2-hydroxyethyl)amino]methyl}-4-methyl-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide



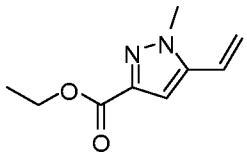
To a solution of 4-chloro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide (Example 8: 20.0 mg, 0.0498 mmol) in tetrahydrofuran (1 mL) was added 2.0 M dimethylzinc in toluene (50 µL, 0.10 mmol). The mixture was purged with nitrogen then stirred in a sealed vial at 110 °C for 2 h. The mixture was cooled to room temperature, concentrated then dissolved in MeOH and purified by prep-HPLC (Acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{21}H_{24}N_3O_2S$ $(M+H)^+$: m/z = 382.2; found 382.1.

Example 10

N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide

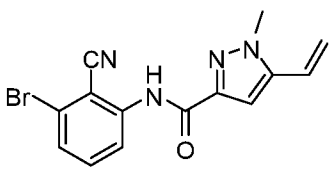


Step 1: ethyl 1-methyl-5-vinyl-1H-pyrazole-3-carboxylate



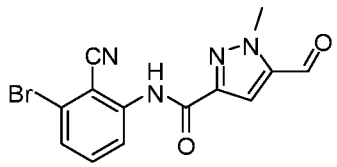
To the mixture of ethyl 5-bromo-1-methyl-1H-pyrazole-3-carboxylate (AstaTech, cat#80198: 500 mg, 2 mmol) in 1,4-dioxane (20 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (730 µL, 4.3 mmol) followed by [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (1:1) (100 mg, 0.1 mmol), sodium carbonate (0.45 g, 4.3 mmol) and water (4 mL). The resulting mixture was purged with nitrogen and stirred at 95 °C for 3 h. The reaction mixture was cooled to room temperature, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 20% AcOEt in DCM to give the desired product. LC-MS calculated for $C_9H_{13}N_2O_2$ $(M+H)^+$: m/z = 181.1; found 181.1.

Step 2: N-(3-bromo-2-cyanophenyl)-1-methyl-5-vinyl-1H-pyrazole-3-carboxamide



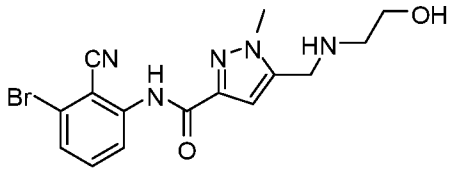
To a mixture of 2-amino-6-bromobenzonitrile (AstaTech, cat#CL8148: 407 mg, 2.06 mmol) and ethyl 1-methyl-5-vinyl-1H-pyrazole-3-carboxylate (310.0 mg, 1.720 mmol) in tetrahydrofuran (20 mL) was added 1.0 M Sodium hexamethyldisilazane in THF (2.06 mL, 2.06 mmol) dropwise at room temperature. The mixture was stirred at room temperature for 1 h then quenched with water and extracted with DCM. The combined extracts were washed with brine then dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with DCM to give the desired product. LC-MS calculated for $C_{14}H_{12}BrN_4O$ $(M+H)^+$: m/z = 331.0; found 331.0.

Step 3: N-(3-bromo-2-cyanophenyl)-5-formyl-1-methyl-1H-pyrazole-3-carboxamide



To a solution of N-(3-bromo-2-cyanophenyl)-1-methyl-5-vinyl-1H-pyrazole-3-carboxamide (0.41 g, 1.2 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added osmium tetraoxide (4wt.% in water, 0.79 mL, 0.12 mmol). The resulting mixture was stirred for 5 min then sodium periodate (794 mg, 3.71 mmol) was added. The mixture was stirred for another 2 h at room temperature and then diluted with DCM, washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 10% AcOEt in DCM to give the desired product. LC-MS calculated for $C_{13}H_{10}BrN_4O_2$ $(M+H)^+$: m/z = 333.0; found 333.0.

Step 4: N-(3-bromo-2-cyanophenyl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide



To a solution of N-(3-bromo-2-cyanophenyl)-5-formyl-1-methyl-1H-pyrazole-3-carboxamide (0.20 g, 0.60 mmol) in methylene chloride (5 mL) was added ethanolamine (140 µL, 2.4 mmol). The mixture was stirred at room temperature for 20 min, then sodium triacetoxyborohydride (300 mg, 1.4 mmol) was added. The reaction mixture was stirred at

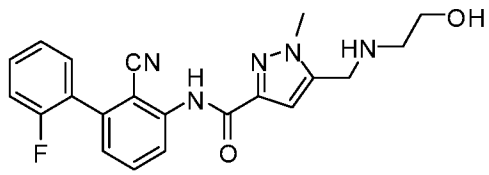
room temperature overnight. LC-MS indicated that some of the imine-intermediate still existed, so $NaBH_4$ (45 mg, 1.2 mmol) and MeOH (2 mL) were added. The mixture was stirred at room temperature for another 2 h and then concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 15% MeOH in DCM to give the desired product. LC-MS calculated for $C_{15}H_{17}BrN_5O_2$ $(M+H)^+$: m/z = 378.1; found 378.0.

Step 5: N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide

A mixture of N-(3-bromo-2-cyanophenyl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide (10 mg, 0.03 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzodioxine (14 mg, 0.053 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.9 mg, 0.001 mmol) and sodium carbonate (3.8 mg, 0.036 mmol) in 1,4-dioxane (1 mL) and water (0.2 mL) was purged with N_2 then stirred at 95 °C overnight. The reaction mixture was cooled to room temperature, diluted with MeOH, filtered and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{24}N_5O_4$ $(M+H)^+$: m/z = 434.2; found 434.2.

Example 11

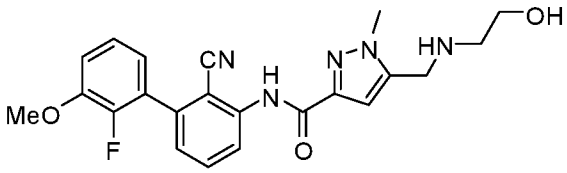
N-(2-cyano-2'-fluorobiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide



This compound was prepared using similar procedures as described for Example 10, Step 5 with 2-fluorophenylboronic acid (Aldrich, cat#445223) replacing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzodioxine. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{21}FN_5O_2$ $(M+H)^+$: m/z = 394.2; found 394.1.

Example 12

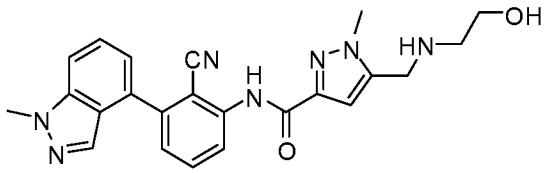
N-(2-cyano-2'-fluoro-3'-methoxybiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide



This compound was prepared using similar procedures as described for Example 10, Step 5 with 2-Fluoro-3-methoxyphenylboronic acid (Aldrich, cat#594253) replacing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzodioxine. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{23}FN_5O_3$ $(M+H)^+$: m/z = 424.2; found 424.2.

Example 13

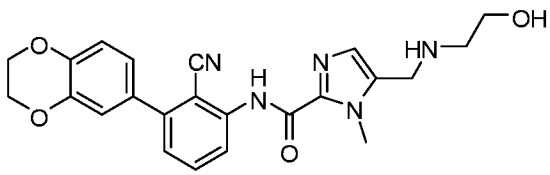
N-[2-cyano-3-(1-methyl-1H-indazol-4-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide



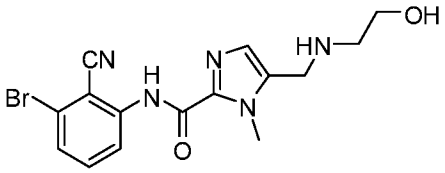
This compound was prepared using similar procedures as described for Example 10, Step 5 with 1-Methylindazole-4-boronic acid (AstaTech, cat#64580) replacing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzodioxine. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{24}N_7O_2$ $(M+H)^+$: m/z = 430.2; found 430.2.

Example 14

N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide



Step 1: N-(3-bromo-2-cyanophenyl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide



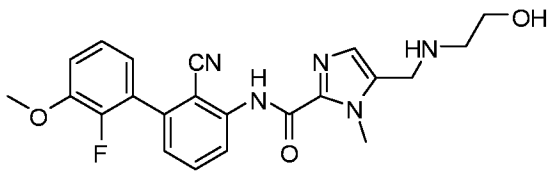
This compound was prepared using similar procedures as described for Example 10, Step 1-4 with ethyl 5-bromo-1-methyl-1H-imidazole-2-carboxylate (Anichem, cat#K20110) replacing ethyl 5-bromo-1-methyl-1H-pyrazole-3-carboxylate in Step 1. The crude product was purified by flash chromatography on a silica gel column eluting with 15% MeOH in DCM to give the desired product. LC-MS calculated for $C_{15}H_{17}BrN_5O_2$ $(M+H)^+$: m/z = 378.1; found 378.0.

Step 2: N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide

A mixture of N-(3-bromo-2-cyanophenyl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide (10 mg, 0.03 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzodioxine (14 mg, 0.053 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.9 mg, 0.001 mmol) and sodium carbonate (3.8 mg, 0.036 mmol) in 1,4-dioxane (1 mL) and water (0.2 mL) was purged with nitrogen then stirred at 95 °C overnight. The reaction mixture was cooled to room temperature, diluted with methanol, filtered then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{24}N_5O_4$ $(M+H)^+$: m/z = 434.2; found 434.2.

Example 15

N-(2-cyano-2'-fluoro-3'-methoxybiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide

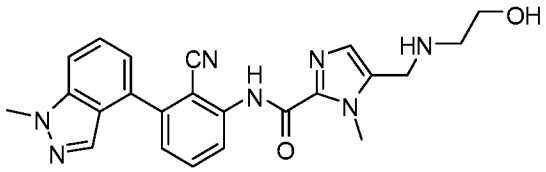


This compound was prepared using similar procedures as described for Example 14, Step 2 with 2-Fluoro-3-methoxyphenylboronic acid (Aldrich, cat#594253) replacing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzodioxine. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired

product as the TFA salt. LC-MS calculated for $C_{22}H_{23}FN_5O_3$ $(M+H)^+$: m/z = 424.2; found 424.1.

Example 16

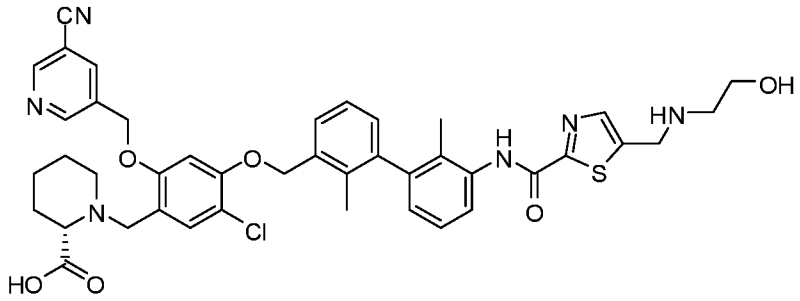
N-[2-cyano-3-(1-methyl-1H-indazol-4-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide



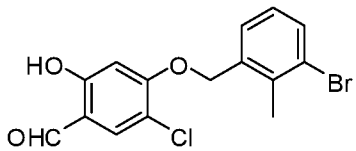
This compound was prepared using similar procedures as described for Example 15, Step 2 with 1-Methylindazole-4-boronic acid (AstaTech, cat#64580) replacing 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzodioxine. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{24}N_7O_2$ $(M+H)^+$: m/z = 430.2; found 430.1.

Example 17

(S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-(((2-hydroxyethyl)amino)methyl)thiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid



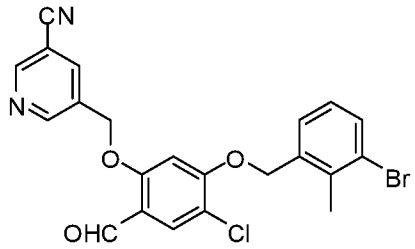
Step 1: 4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-hydroxybenzaldehyde



To a mixture of (3-bromo-2-methylphenyl)methanol (2.33 g, 11.59 mmol), 5-chloro-2,4-dihydroxybenzaldehyde (2.0 g, 11.59 mmol) and triphenylphosphine (3.65 g, 13.91 mmol) in THF (10 ml) at 0 °C was added DIAD (2.93 ml, 15.07 mmol). The mixture was stirred at room temperature overnight. The mixture was concentrated and diluted with EtOAc.

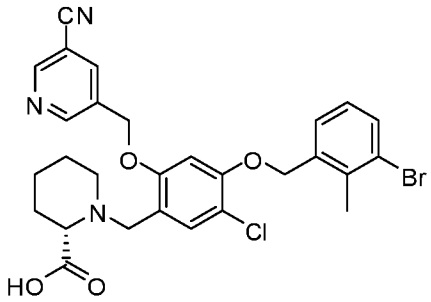
The solid was collected by filtration to give 4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-hydroxybenzaldehyde (2.0 g, 5.62 mmol, 48.5 % yield). LCMS calculated for $C_{15}H_{13}BrClO_3$ $(M+H)^+$: m/z = 355.0; found 355.2.

Step 2: 5-((5-((3-bromo-2-methylbenzyl)oxy)-4-chloro-2-formylphenoxy)methyl)nicotinonitrile



A mixture of 4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-hydroxybenzaldehyde (2.0 g, 5.62 mmol), 5-(chloromethyl)nicotinonitrile (0.927 g, 6.07 mmol) and cesium carbonate (2.75 g, 8.44 mmol) in DMF (12 ml) was stirred at 70 °C for 3 hours. The mixture was cooled to room temperature and then poured into water. The solid was collected by filtration and air dried to give 5-((5-((3-bromo-2-methylbenzyl)oxy)-4-chloro-2-formylphenoxy)methyl)nicotinonitrile (2.2 g, 4.66 mmol, 83 % yield). LCMS calculated for $C_{22}H_{17}BrClN_2O_3$ (M+H)+: m/z = 471.0; found 471.2.

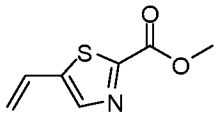
Step 3: (S)-1-(4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-((5-cyanopyridin-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid



Sodium triacetoxyborohydride (158 mg, 0.746 mmol) was added to a mixture of 5-((5-((3-bromo-2-methylbenzyl)oxy)-4-chloro-2-formylphenoxy)methyl)nicotinonitrile (176 mg, 0.373 mmol), (S)-piperidine-2-carboxylic acid (72.3 mg, 0.560 mmol) and triethylamine (0.156 ml, 1.119 mmol) in DCM (1.0 ml). After stirring at room temperature overnight, the mixture was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt (150 mg). LCMS calculated for $C_{28}H_{28}BrClN_3O_4$ (M+H)+: m/z =

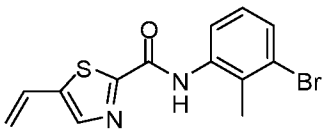
584.1; found 584.1.

Step 4: methyl 5-vinylthiazole-2-carboxylate



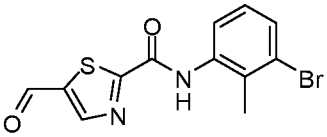
Methyl 5-bromothiazole-2-carboxylate (0.72 g, 3.24 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.55 ml, 3.24 mmol), tetrakis(triphenylphosphine)palladium(0) (0.375 g, 0.324 mmol) and potassium carbonate (0.896 g, 6.48 mmol) were weighed into a microwave vial. 1,4-Dioxane (3 ml) and water (0.6 ml) were added and the mixture was purged with N_2 for 5 min. The mixture was heated at 100 °C for 2 h and then cooled to room temperature and concentrated. The residue was purified on silica gel column (0-100% EtOAc/Hexanes) to give methyl 5-vinylthiazole-2-carboxylate (0.3 g, 1.773 mmol, 54.7 % yield). LCMS calculated for $C_7H_8NO_2S$ (M+H)+: m/z = 170.0; found 170.0.

Step 5: N-(3-bromo-2-methylphenyl)-5-vinylthiazole-2-carboxamide



1.0 M THF solution of potassium tert-butoxide (5.32 mL, 5.32 mmol) was added to a solution of methyl 5-vinylthiazole-2-carboxylate (0.3 g, 1.773 mmol) and 3-bromo-2-methylaniline (0.24 mL, 1.950 mmol) in THF (5 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched with water, extracted with ethyl acetate, concentrated and purified on silica gel column (0-100% EtOAc/Hexanes) to give N-(3-bromo-2-methylphenyl)-5-vinylthiazole-2-carboxamide (0.4 g, 1.238 mmol, 69.8 % yield). LCMS calculated for $C_{13}H_{12}BrN_2OS$ (M+H)+: m/z = 323.0; found 323.0.

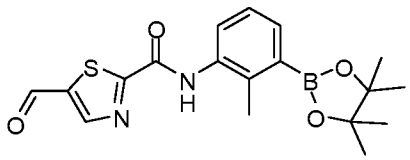
Step 6: N-(3-bromo-2-methylphenyl)-5-formylthiazole-2-carboxamide



To a mixture of N-(3-bromo-2-methylphenyl)-5-vinylthiazole-2-carboxamide (0.22 g, 0.681 mmol) in THF (4 ml)/Water (1 ml) cooled in an ice bath was added 4% water solution of osmium tetroxide (0.83 ml, 0.136 mmol). The reaction was stirred for 5 min and then

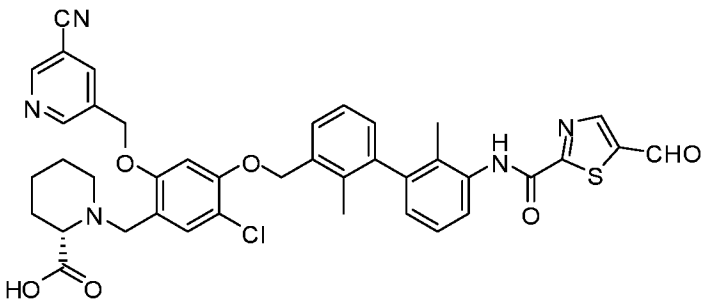
sodium periodate (0.437 g, 2.042 mmol) was added. After stirring at room temperature overnight, the reaction was quenched with saturated aqueous solution of sodium thiosulfate. The mixture was then extracted with DCM, concentrated in vacuo and purified on silica gel column (0-100% EtOAc in hexanes) to give N-(3-bromo-2-methylphenyl)-5-formylthiazole-2-carboxamide (0.19 g, 0.584 mmol, 86 % yield). LCMS calculated for $C_{12}H_{10}BrN_2O_2S$ (M+H)+: m/z = 325.0; found 325.0.

Step 7: 5-formyl-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiazole-2-carboxamide



A mixture of N-(3-bromo-2-methylphenyl)-5-formylthiazole-2-carboxamide (0.17 g, 0.523 mmol), bis(pinacolato)diboron (0.199 g, 0.784 mmol), potassium acetate (0.103 g, 1.046 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.043 g, 0.052 mmol) was purged with nitrogen and then 1,4-dioxane (4 ml) was added. The resulting mixture was stirred at 100 °C for 2 h and then cooled to room temperature and concentrated. The residue was purified on silica gel column (0-100% EtOAc/Hexanes) to give 5-formyl-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiazole-2-carboxamide (0.17 g, 0.457 mmol, 87 % yield). LCMS calculated for $C_{18}H_{22}BN_2O_4S$ (M+H)+: m/z = 373.1; found 373.1.

Step 8: (S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-formylthiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid



A mixture of (S)-1-(4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-((5-cyanopyridin-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid (24 mg, 0.04 mmol), 5-formyl-N-(2-

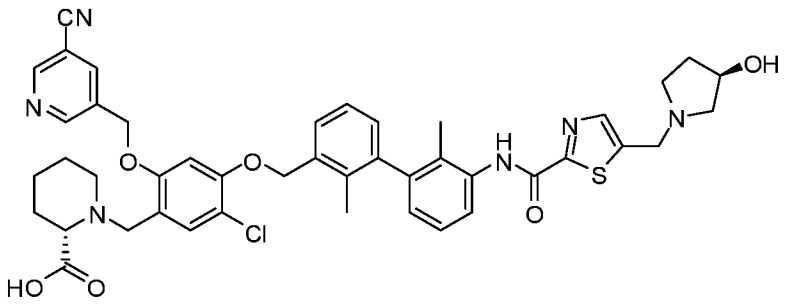
methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiazole-2-carboxamide (15 mg, 0.040 mmol), potassium carbonate (11 mg, 0.08 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.7 mg, 4.0 μmol) in 1,4-dioxane (2 ml) and water (1 ml) was purged with nitrogen, and then heated at 100 °C for 2 h. After cooled to room temperature, the mixture was concentrated and the residue was purified on silica gel column (0-15% MeOH/DCM) to give (S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-formylthiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid (20 mg, 0.027 mmol, 66.2 % yield). LCMS calculated for $C_{40}H_{37}ClN_5O_6S$ (M+H)+: m/z = 750.2; found 750.2.

Step 9: (S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-(((2-hydroxyethyl)amino)methyl)thiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid

A mixture of (S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-formylthiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid (6 mg, 8.00 μmol) and 2-aminoethan-1-ol (0.5 mg, 8.00 μmol) in DCM (1.0 ml) was stirred for 30 min at room temperature and then sodium triacetoxyborohydride (2.5 mg, 0.012 mmol) was added. After stirring at room temperature for 2 h, the mixture was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LCMS calculated for $C_{42}H_{44}ClN_6O_6S$ (M+H)+: m/z = 795.3; found 795.3.

Example 18

(S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)thiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid

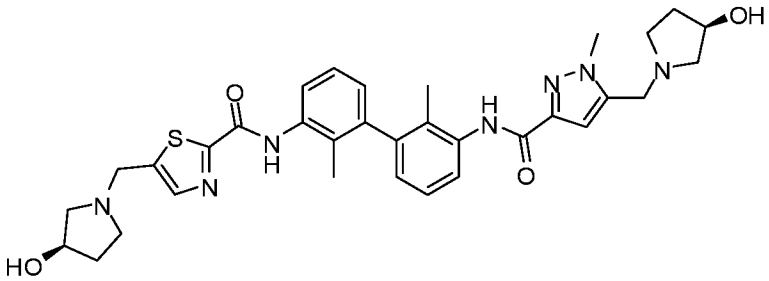


This compound was prepared using similar procedures as described for Example 17, Step 9 with (R)-pyrrolidin-3-ol replacing 2-aminoethan-1-ol. The reaction mixture was

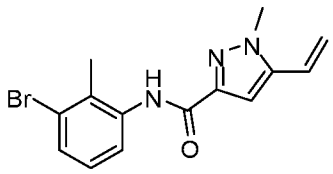
purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{44}H_{46}ClN_6O_6S$ (M+H)+: m/z = 821.3; found 821.3.

Example 19

5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-N-(3'-(5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)thiazole-2-carboxamide

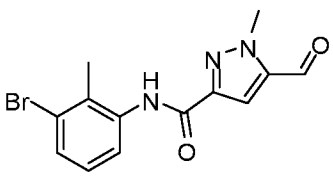


Step 1: N-(3-bromo-2-methylphenyl)-1-methyl-5-vinyl-1H-pyrazole-3-carboxamide



1M THF solution of potassium tert-butoxide (4.16 mL, 4.16 mmol) was added to a solution of ethyl 1-methyl-5-vinyl-1H-pyrazole-3-carboxylate (Example 10, Step 1: 0.25 g, 1.387 mmol) and 3-bromo-2-methylaniline (0.188 mL, 1.526 mmol) in THF (5 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched with water, extracted with ethyl acetate, concentrated and purified on silica gel column (0-100% EtOAc/Hexanes) to give N-(3-bromo-2-methylphenyl)-1-methyl-5-vinyl-1H-pyrazole-3-carboxamide (0.4 g, 1.249 mmol, 90 % yield). LCMS calculated for $C_{14}H_{15}BrN_3O$ (M+H)+: m/z = 320.0; found 320.0.

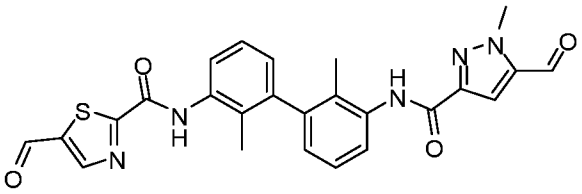
Step 2: N-(3-bromo-2-methylphenyl)-5-formyl-1-methyl-1H-pyrazole-3-carboxamide



To a mixture of N-(3-bromo-2-methylphenyl)-1-methyl-5-vinyl-1H-pyrazole-3-carboxamide (0.4 g, 1.25 mmol) in THF (10 ml) and water (2.5 ml) cooled in an ice bath was added 4% aq. osmium tetroxide (1.53 ml, 0.25 mmol). The reaction mixture was stirred for 5

min and then sodium periodate (0.802 g, 3.75 mmol) was added. After stirring at room temperature for 1 h, the reaction was quenched with sat. aq. solution of sodium thiosulfate. The mixture was then extracted with DCM, concentrated in vacuo and purified on silica gel column (0-100% EtOAc/Hexanes) to give N-(3-bromo-2-methylphenyl)-5-formyl-1-methyl-1H-pyrazole-3-carboxamide (0.29 g, 0.900 mmol, 72.1 % yield). LCMS calculated for $C_{13}H_{13}BrN_3O_2$ $(M+H)^+$: m/z = 322.0; found 322.0.

Step 3: 5-formyl-N-(3'-(5-formyl-1-methyl-1H-pyrazole-3-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)thiazole-2-carboxamide



A mixture of N-(3-bromo-2-methylphenyl)-5-formyl-1-methyl-1H-pyrazole-3-carboxamide (17.31 mg, 0.054 mmol), 5-formyl-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiazole-2-carboxamide (Example 17, Step 7: 20 mg, 0.054 mmol), potassium carbonate (15 mg, 0.11 mmol) and tetrakis(triphenylphosphine)palladium(0) (6.2 mg, 5.4 μmol) in 1,4-dioxane (3 ml) and water (0.6 ml) was purged with nitrogen, and heated at 100 °C for 2 h. The mixture was purified on silica gel column (0-100% EtOAc/Hexanes) to give 5-formyl-N-(3'-(5-formyl-1-methyl-1H-pyrazole-3-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)thiazole-2-carboxamide (20 mg, 0.041 mmol, 76 % yield). LCMS calculated for $C_{25}H_{22}N_5O_4S$ $(M+H)+$: m/z = 488.1; found 488.1.

Step 4: 5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-N-(3'-(5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)thiazole-2-carboxamide

A mixture of 5-formyl-N-(3'-(5-formyl-1-methyl-1H-pyrazole-3-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)thiazole-2-carboxamide (20 mg, 0.041 mmol) and (R)-pyrrolidin-3-ol (7.9 mg, 0.09 mmol) in DCM (1.0 ml) was stirred for 30 min at room temperature then sodium triacetoxyborohydride (26.1 mg, 0.123 mmol) was added. After stirring at room temperature for 2 h, the mixture was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LCMS calculated for $C_{33}H_{40}N_7O_4S$ $(M+H)+$: m/z = 630.3; found 630.3.

Example A. PD-1/PD-L1 Homogeneous Time-Resolved Fluorescence (HTRF) binding assay

The assays were conducted in a standard black 384-well polystyrene plate with a final volume of 20 μL. Inhibitors were first serially diluted in DMSO and then added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 1%. The assays were carried out at 25° C in the PBS buffer (pH 7.4) with 0.05% Tween-20 and 0.1% BSA. Recombinant human PD-L1 protein (19-238) with a His-tag at the C-terminus was purchased from AcroBiosystems (PD1-H5229). Recombinant human PD-1 protein (25-167) with Fc tag at the C-terminus was also purchased from AcroBiosystems (PD1-H5257). PD-L1 and PD-1 proteins were diluted in the assay buffer and 10 μL was added to the plate well. Plates were centrifuged and proteins were preincubated with inhibitors for 40 minutes. The incubation was followed by the addition of 10 μL of HTRF detection buffer supplemented with Europium cryptate-labeled anti-human IgG (PerkinElmer-AD0212) specific for Fc and anti-His antibody conjugated to SureLight®-Allophycocyanin (APC, PerkinElmer-AD0059H). After centrifugation, the plate was incubated at 25° C for 60 min. before reading on a PHERAstar FS plate reader (665nm/620nm ratio). Final concentrations in the assay were - 3 nM PD1, 10 nM PD-L1, 1 nM europium anti-human IgG and 20 nM anti-His-Allophycocyanin.IC_{50} determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the GraphPad Prism 5.0 software.

Compounds of the present disclosure, as exemplified in the Examples, showed IC_{50} values in the following ranges: + = $IC_{50} \leq 100$ nM; ++ = 100 nM < $IC_{50} \leq 500$ nM; +++ = 500 nM < $IC_{50} \leq 10000$ nM

Data obtained for the Example compounds using the PD-1/PD-L1 homogenous time-resolved fluorescence (HTRF) binding assay described in Example A is provided in Table 1.

Table 1

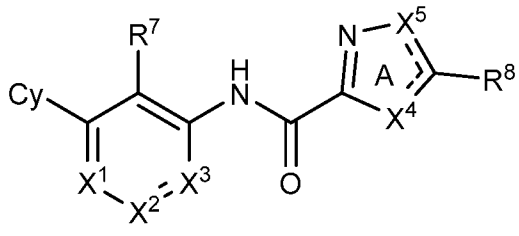
Example	PD-1/PD-L1 HTRF IC_{50} (nM)
1	+
2	+
3	++
4	++
5	+
6	+

7	+
8	+
9	+
10	+
11	+
12	+
13	+
14	+
15	+
16	++
17	+
18	+
19	+

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 without limitation 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 or a stereoisomer thereof, wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10}cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, $-P(O)R^{10}R^{10}$, $-P(O)(OR^{10})(OR^{10})$, $-B(OH)_2$, $-B(OR^{10})_2$ and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aC(=NOH)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from B, P, N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, $-P(O)R^{11}R^{11}$, $-P(O)(OR^{11})(OR^{11})$, $-B(OH)_2$, $-B(OR^{11})_2$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered

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

R^8 is halo, ethyl, propyl, isopropyl, butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, -NHR^9, -NR^9R^{11}, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, -$P(O)R^{11}R^{11}$, -$P(O)(OR^{11})(OR^{11})$, -$B(OH)_2$, -$B(OR^{11})_2$, or $S(O)_2NR^{11}R^{11}$, wherein the butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{5-6} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10

membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$, $-P(O)R^cR^c$, $-P(O)(OR^c)(OR^c)$, $-B(OH)_2$, $-B(OR^c)_2$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered

heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, NHOR^c, OR^c, SR^c, C(O)R^c, C(O)NR^{c}R^c, C(O)OR^c, OC(O)R^c, OC(O)NR^{c}R^c, C(=NR^c)NR^{c}R^c, NR^{c}C(=NR^c)NR^{c}R^c, NR^{c}C(=NOH)NR^{c}R^c, NR^{c}C(=NCN)NR^{c}R^c, NHR^c, NR^{c}R^c, NR^{c}C(O)R^c, NR^{c}C(O)OR^c, NR^{c}C(O)NR^{c}R^c, NR^{c}S(O)R^c, NR^{c}S(O)$_2$R^c, NR^{c}S(O)$_2$NR^{c}R^c, S(O)R^c, S(O)NR^{c}R^c, S(O)$_2$R^c, -P(O)R^{c}R^c, -P(O)(OR^c)(OR^c), -B(OH)$_2$, -B(OR^c)$_2$ and S(O)$_2$NR^{c}R^c; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^c 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, NHOR^g, OR^g, SR^g, C(O)R^g, C(O)NR^{g}R^g, C(O)OR^g, OC(O)R^g, OC(O)NR^{g}R^g, NHR^g, NR^{g}R^g, NR^{g}C(O)R^g, NR^{g}C(O)NR^{g}R^g, NR^{g}C(O)OR^g, C(=NR^g)NR^{g}R^g, NR^{g}C(=NR^g)NR^{g}R^g, NR^{g}C(=NOH)NR^{g}R^g, NR^{g}C(=NCN)NR^{g}R^g, S(O)R^g, S(O)NR^{g}R^g, S(O)$_2$R^g, NR^{g}S(O)$_2$R^g, NR^{g}S(O)$_2$NR^{g}R^g, -P(O)R^{g}R^g, -P(O)(OR^g)(OR^g), -B(OH)$_2$, -B(OR^g)$_2$ and S(O)$_2$NR^{g}R^g; wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl,

C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, $NR^oC(O)OR^o$, $C(=NR^o)NR^oR^o$, $NR^oC(=NR^o)NR^oR^o$, $S(O)R^o$, $S(O)NR^oR^o$, $S(O)_2R^o$, $NR^oS(O)_2R^o$, $NR^oS(O)_2NR^oR^o$, $-P(O)R^oR^o$, $-P(O)(OR^o)(OR^o)$, $-B(OH)_2$, $-B(OR^o)_2$ and $S(O)_2NR^oR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, $-P(O)R^eR^e$, $-P(O)(OR^e)(OR^e)$, $-B(OH)_2$, $-B(OR^e)_2$ and $S(O)_2NR^eR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are

each optionally substituted with 1-3 R^p substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, $NR^rC(O)R^r$, $NR^rC(O)NR^rR^r$, $NR^rC(O)OR^r$, $C(=NR^r)NR^rR^r$, $NR^rC(=NR^r)NR^rR^r$, $NR^rC(=NOH)NR^rR^r$, $NR^rC(=NCN)NR^rR^r$, $S(O)R^r$, $S(O)NR^rR^r$, $S(O)_2R^r$, $NR^rS(O)_2R^r$, $NR^rS(O)_2NR^rR^r$, $-P(O)R^rR^r$, $-P(O)(OR^r)(OR^r)$, $-B(OH)_2$, $-B(OR^r)_2$ and $S(O)_2NR^rR^r$, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{6-10} aryl-C_{1-4} alkyl-, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NHR^i, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $NR^iC(=NOH)NR^iR^i$, $NR^iC(=NCN)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, $-P(O)R^iR^i$, $-P(O)(OR^i)(OR^i)$, $-B(OH)_2$, $-B(OR^i)_2$ and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, $-P(O)R^kR^k$, $-P(O)(OR^k)(OR^k)$, $-B(OH)_2$, $-B(OR^k)_2$ and $S(O)_2NR^kR^k$, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, and C_{1-}

4 haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl, taken together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^q substituents;

or any two R^k substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^q substituents;

or any two R^o substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^{10} substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

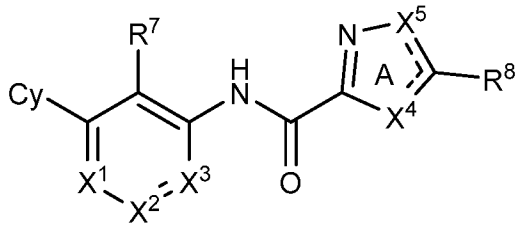
or any two R^{11} substituents together with the nitrogen, phosphorus or boron atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^q are each optionally substituted with halo, OH, CN, -COOH, NH_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl; and

⎓is a single bond or a double bond to maintain ring A being aromatic.

2. The compound of claim **1**, having Formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10}cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NHR^{10}, -$NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aC(=NOH)NR^aR^a$, $NR^aC(=NCN)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, and $S(O)_2NR^aR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered

heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, ethyl, propyl, isopropyl, butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the butyl, 2-butyl, 2-methylpropyl, C_{5-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4}

alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{5-6} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents.

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

cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $NR^gC(=NOH)NR^gR^g$, $NR^gC(=NCN)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, $NR^oC(O)OR^o$, $C(=NR^o)NR^oR^o$, $NR^oC(=NR^o)NR^oR^o$, $S(O)R^o$, $S(O)NR^oR^o$, $S(O)_2R^o$, $NR^oS(O)_2R^o$, $NR^oS(O)_2NR^oR^o$, and $S(O)_2NR^oR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $NR^eC(=NOH)NR^eR^e$, $NR^eC(=NCN)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

each R^e 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-

, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^e are each optionally substituted with 1, 2 or 3 independently selected R^f substituents;

each R^g 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, $NR^rC(O)R^r$, $NR^rC(O)NR^rR^r$, $NR^rC(O)OR^r$, $C(=NR^r)NR^rR^r$, $NR^rC(=NR^r)NR^rR^r$, $NR^rC(=NOH)NR^rR^r$, $NR^rC(=NCN)NR^rR^r$, $S(O)R^r$, $S(O)NR^rR^r$, $S(O)_2R^r$, $NR^rS(O)_2R^r$, $NR^rS(O)_2NR^rR^r$ and $S(O)_2NR^rR^r$, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{6-10} aryl-C_{1-4} alkyl-, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, NHR^i, NR^iR^i, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $NR^iC(=NOH)NR^iR^i$, $NR^iC(=NCN)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each optionally substituted by 1, 2, or 3 R^j

substituents independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl, taken together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^g substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^i substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^k substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^o substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$, wherein the C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^q are each optionally substituted with halo, OH, CN, -COOH, NH_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl; and

-----is a single bond or a double bond to maintain ring A being aromatic.

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

any two R^i substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or any two R^k substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^q.

4. The compound of any one of claims **1-3**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

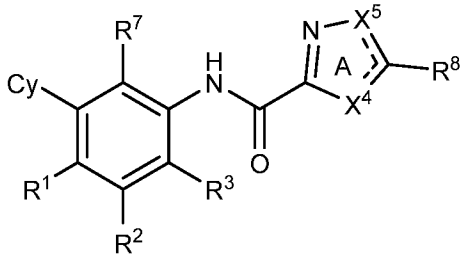
R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$,

$C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NOH)NR^{11}R^{11}$, $NR^{11}C(=NCN)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents; and

R^9 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{b1} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, $NR^cC(=NOH)NR^cR^c$, $NR^cC(=NCN)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

5. The compound of any one of claims **1-4**, having Formula (II):

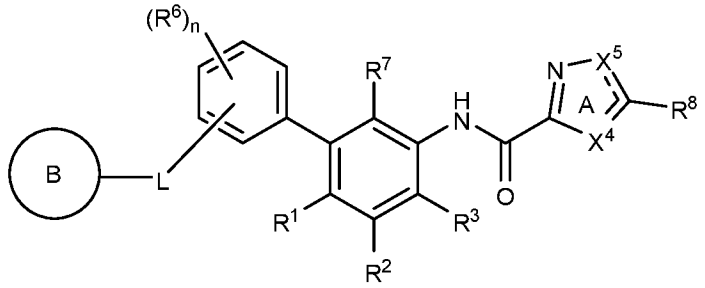


(II)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

6. The compound of any one of claims **1-4**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein (i) X^1 is N, X^2 is CR^2 and X^3 is CR^3; (ii) X^1 is CR^1, X^2 is N and X^3 is CR^3; (iii) X^1 is CR^1, X^2 is CR^2 and X^3 is N; (iv) X^1 is N, X^2 is CR^2 and X^3 is N; (v) X^1 is N, X^2 is N and X^3 is CR^3; or (vi) X^1 is CR^1, X^2 is N and X^3 is N.

7. The compound of any one of claims **1-5**, having Formula (III):



(III)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

L is a bond, $-C(O)NR^{13}$-, $-NR^{13}C(O)$-, O, $-(CR^{14}R^{15})_q$-, $-(CR^{14}R^{15})_q$-O-, $-O(CR^{14}R^{15})_q$-, $-NR^{13}$-, $-(CR^{14}R^{15})_q-NR^{13}$-, $-NR^{13}-(CR^{14}R^{15})_q$-, -CH=CH-, —C≡C—, $-SO_2NR^{13}$-, $-NR^{13}SO_2$-, $-NR^{13}SO_2NR^{13}$-, $-NR^{13}C(O)O$-, $-OC(O)NR^{13}$ or $-NR^{13}C(O)NR^{13}$-;

each R^{13} is independently H, C_{1-6} haloalkyl or C_{1-6} alkyl optionally substituted with a substituent selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, halo, OH, -COOH, NH_2, $-NHC_{1-4}$ alkyl and $-N(C_{1-4}$ alkyl$)_2$;

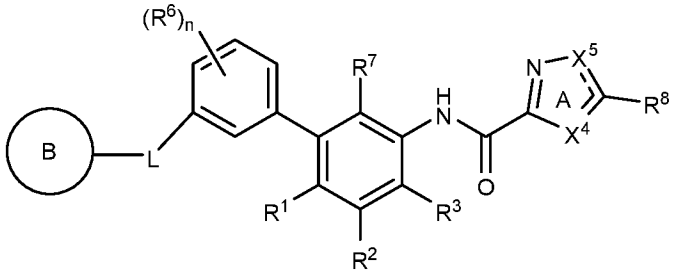
R^{14} and R^{15} are each independently selected from H, halo, CN, OH, -COOH, C_{1-4} alkyl, C_{1-4} alkoxy, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl$)_2$, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^{14} or R^{15} are each optionally substituted with 1, 2, or 3 independently selected R^q substituents;

or R^{14} and R^{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R^q substituents;

ring B is C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2 or 3 independently selected R^d substituents; and

the subscript n is an integer of 1, 2, 3 or 4.

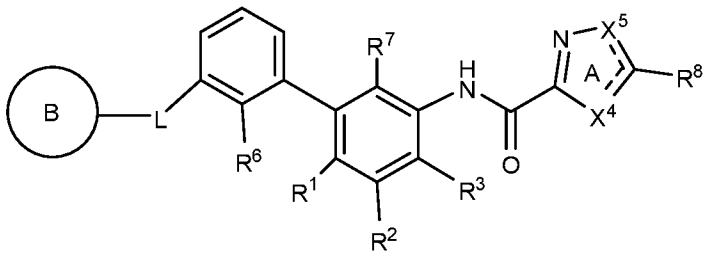
8. The compound of any one of claims **1-5** and **7**, having Formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

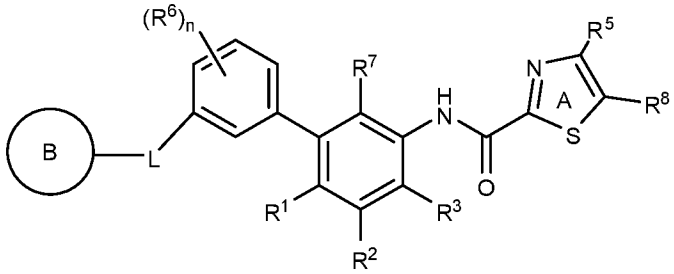
9. The compound of any one of claims **1-5** and **7-8**, having Formula (IIIa-1):



(IIIa-1)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

10. The compound of any one of claims **1-5** and **7**, having Formula (IIIa-2):

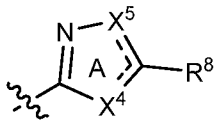


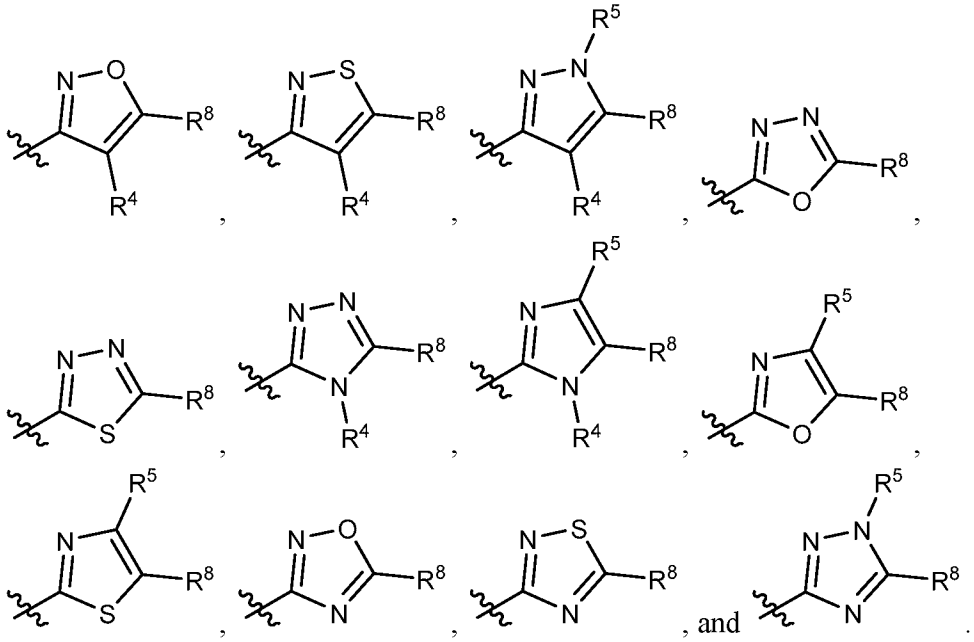
(IIIa-2)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

11. The compound of any one of claims **7-10**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^d is C_{1-6} alkyl, phenyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, OR^e, $C(O)R^e$, halo or CN, wherein the C_{1-6} alkyl, phenyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1, 2 or 3 independently selected R^f substituents.

12. The compound of any one of claims **7-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^d is (3-carboxypyrrolidin-1-yl)methyl, (R)-(3-carboxypyrrolidin-1-yl)methyl, (S)-(3-carboxypyrrolidin-1-yl)methyl, (3-hydroxypyrrolidin-1-yl)methyl, (R)-(3-hydroxypyrrolidin-1-yl)methyl, (S)-(3-hydroxypyrrolidin-1-yl)methyl, (2-hydroxyethylamino)methyl, (2-hydroxy-2-methylpropylamino)methyl, 2-(dimethylamino)ethanoyl, 2-(3-carboxyazetidin-1-yl)ethanoyl, (R)-2-(3-carboxyazetidin-1-yl)ethanoyl, (S)-2-(3-carboxyazetidin-1-yl)ethanoyl, 2-(2-carboxypiperidin-1-yl)ethanoyl, (R)-2-(2-carboxypiperidin-1-yl)ethanoyl, (S)-2-(2-carboxypiperidin-1-yl)ethanoyl, 2-(3-carboxypyrrolidin-1-yl)ethanoyl, (S)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (R)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (5-cyanopyridin-3-yl)methoxy, (2-hydroxyethylamino)methyl, 2-carboxy-1-piperidinylmethyl, (S)-2-carboxy-1-piperidinylmethyl, (R)-2-carboxy-1-piperidinylmethyl, halo or CN.

13. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the moiety  is selected from:



14. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein (i) X^4 is S and X^5 is CR^5; (ii) X^4 is O and X^5 is CR^5; (iii) X^4 is NR^4 and X^5 is CR^5; or (iv) X^4 is CR^4 and X^5 is NR^5.

15. The compound of any one of claims **1-6** and **13-14** or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein Cy is phenyl, 5- or 6-membered heteroaryl, C_{3-6} cycloalkyl or 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents; or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents.

16. The compound of any one of claims **1-6** and **13-14**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein Cy is phenyl, 2-thiophenyl, 3-thiophenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3,6-dihydro-2H-pyran-4-yl, cyclohexyl, cyclohexenyl, 2,3-dihydro-1,4-

benzodioxin-6-yl, 1,3-benzodioxin-5-yl, 2-methylindazol-6-yl or 1-methylindazol-4-yl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents.

17. The compound of any one of claims **1-6** and **13-14**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein Cy is phenyl optionally substituted with 1 to 5 independently selected R^6 substituents.

18. The compound of any one of claims **1-6** and **13-14**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein Cy is phenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-fluorophenyl, 2-fluoro-3-methoxyphenyl, or 1-methyl-1H-indazol-4-yl.

19. The compound of any one of claims **1-18**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 groups-independently selected from halo, OH, CN and C_{1-4} alkoxy.

20. The compound of any one of claims **1-19**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^4 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl or C_{1-6} haloalkoxy.

21. The compound of any one of claims **1-20**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^5 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl or C_{1-6} haloalkoxy.

22. The compound of any one of claims **1-17** and **19-21**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^6 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, OR^a, $C(O)NR^aR^a$, or $NR^aC(O)R^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents; or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents.

23. The compound of any one of claims **1-17** and **19-21**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^6 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, or OR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents; or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents.

24. The compound of any one of claims **1-23**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl or phenyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

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

25. The compound of any one of claims **1-24**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^8 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents or (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- optionally substituted with 1, 2 or 3 independently selected R^b substituents.

26. The compound of any one of claims **1-24**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^8 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents.

27. The compound of any one of claims **1-24**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^8 is $–CH_2NHR^c$ or $–CH_2NR^cR^c$.

28. The compound of any one of claims **1-24**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^8 is (2-hydroxyethylamino)methyl, 2-carboxy-1-piperidinylmethyl, (S)-2-carboxy-1-piperidinylmethyl, (R)-2-carboxy-1-piperidinylmethyl, or 3-hydroxypyrrolidin-1-ylmethyl.

29. The compound of any one of claims **1-24**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^8 is (2-hydroxyethylamino)methyl, 2-carboxy-1-piperidinylmethyl, (S)-2-carboxy-1-piperidinylmethyl, or (R)-2-carboxy-1-piperidinylmethyl.

30. The compound of claim **1**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is phenyl, C_{3-6} cycloalkyl, 5- to 6-membered heteroaryl, or 4- to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused 5-, 6- or 7-membered heterocycloalkyl ring, or a fused 5- or 6-membered heteroaryl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, COOH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, cyclopropyl, cyclopropylmethyl, phenyl, phenyl-C_{1-4} alkyl-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkyl-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, NH_2, -NHC_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, -C(O)R^{10}, -O(CO)R^{10}, -C(O)OR^{10}, -O(CO)NHR^{10}, -NHC(O)OR^{10}, -NHC(O)NHR^{10}, -C(O)NHR^{10}, -NHC(O)R^{10}, -SO_2R^{10}, -NHSO_2R^{10} and -SO_2NHR^{10}, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, cyclopropyl, cyclopropylmethyl, phenyl, phenyl-C_{1-4} alkyl-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkyl-, 4-6 membered heterocycloalkyl and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2 or R^3 are each optionally substituted with halo, OH, CN or C_{1-4} alkoxy;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- or (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, COOH, NO_2, OR^a, C(O)OR^a, NH_2, -NHR^a, -N(R^a)$_2$, -C(O)R^a, -O(CO)R^a, -C(O)OR^a, -O(CO)N$R^a$$R^a$, -NHC(O)O$R^a$, -NHC(O)N$R^a$$R^a$, -C(O)N$R^a$$R^a$, -NHC(O)$R^a$, -$SO_2R^a$, -NH$SO_2R^a$ and -SO_2N$R^a$$R^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^4, R^5 and R^6 are each optionally substituted with 1 or 2 R^b substituents;

R^7 is halo, C_{1-6} alkyl, CN, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- and (5-6 membered heteroaryl)-C_{1-4} alkyl of R^7 are

each optionally substituted with 1 or 2 susbtituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy,CN, OH, NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, COOH, -OC_{1-6} alkyl, -SC_{1-6} alkyl, C(O)NH_2, -C(O)NH(C_{1-6} alkyl), -C(O)NH(C_{1-6} alkyl)$_2$, -C(O)OC_{1-6} alkyl, -OC(O)NHC_{1-6} alkyl, -OC(O)NH_2, -OC(O)NH(C_{1-6} alkyl)$_2$, -NHC(O)C_{1-6} alkyl, -NHC(O)H, -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -NHC(O)OC_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)OC_{1-6} alkyl, -NHC(O)NH(C_{1-6} alkyl), -NHC(O)N(C_{1-6} alkyl)$_2$, -NHC(O)NH_2, -N(C_{1-6} alkyl)C(O)NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)C(O)N(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)C(O)NH_2, -NHS(O)$_2$(C_{1-6} alkyl), -N(C_{1-6} alkyl)S(O)$_2$(C_{1-6} alkyl), -NHS(O)$_2NH_2$, -NHS(O)$_2$NH(C_{1-6} alkyl), -NHS(O)$_2$N(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)S(O)$_2NH_2$, -N(C_{1-6} alkyl)S(O)$_2$NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)S(O)$_2$N(C_{1-6} alkyl)$_2$, -S(O)$_2$(C_{1-6} alkyl), -S(O)$_2NH_2$, -S(O)$_2$NH(C_{1-6} alkyl) and -S(O)$_2$N(C_{1-6} alkyl)$_2$;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, OR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)_2R^{11}$, or $S(O)_2NR^{11}R^{11}$, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents; and

R^9 is C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- or (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} is independently selected from H, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-6

membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1 or 2 R^b substituents;

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

each R^b is independently selected from halo, 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_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OH, NH_2, NHR^c, $N(R^c)_2$, OR^c, $C(O)NR^cR^c$, $C(O)OR^c$, COOH, $NR^cC(O)R^c$, $OC(O)NR^cR^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)_2R^c$ and $S(O)_2NR^cR^c$, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, phenyl-C_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^b are each optionally substituted with 1 or 2 R^d substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, 4-6 membered heterocycloalkyl, (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, 5-6 membered heteroaryl, (5-6 membered heteroaryl)-C_{1-4} alkyl-, CN, OH, COOH, OR^e, $C(O)OR^e$, NH_2, $-NHR^e$, $-N(R^e)_2$, $-C(O)NR^eR^e$, $-NR^eC(O)R^e$, $OC(O)NR^eR^e$, $NR^eC(O)OR^e$, $NR^eC(O)NR^eR^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, $S(O)_2R^e$ and $S(O)_2NR^eR^e$, wherein R^e is H or C_{1-6} alkyl;

each R^c is independently selected from H, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl-, and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl-, 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_{1-4} alkyl-, C_{3-6} cycloalkyl-C_{1-4} alkyl-, (5-6 membered heteroaryl)-C_{1-4} alkyl- and (4-6 membered heterocycloalkyl)-C_{1-4} alkyl- of R^c are each optionally substituted with 1 or 2 R^f substituents;

or two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1 or 2 independently selected R^h substituents;

each R^f is independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered heteroaryl, CN, OH, COOH, OR^g, $C(O)OR^g$, NH_2, $-NHR^g$, $-N(R^g)_2$, $-C(O)NR^gR^g$, $-NR^gC(O)R^g$, $OC(O)NR^gR^g$, $NR^gC(O)OR^g$, $NR^gC(O)NR^gR^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, $S(O)_2R^g$ and $S(O)_2NR^gR^g$, wherein each R^g is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; and

each R^h is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, NHR^i, $N(R^i)_2$, OR^i, $C(O)NR^iR^i$, $NR^iC(O)R^i$ and $C(O)OR^i$, wherein R^i is H or C_{1-6} alkyl.

31. The compound of claim **1**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is O, S, N, NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NHR^{10}$, $-NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, and $NR^{10}C(O)OR^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^1, R^2, R^3 and R^{10} are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered

heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)NR^aR^a$, NHR^a, NR^aR^a, $NR^aC(O)R^a$, and $NR^aC(O)OR^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, and $NR^{11}C(O)OR^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, C_{7-10} aryl, cyclopropyl substituted with 1-3 independently selected R^b substituents, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^9$, $-NR^9R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, or $NR^{11}C(O)OR^{11}$, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{7-10} aryl, C_{4-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 is methyl, ethyl, propyl, isopropyl, C_{5-6} alkyl, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl, wherein the C_{5-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10

membered heteroaryl, and 4-10 membered heterocycloalkyl of R^9 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, and $OC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, and $NR^cC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents.

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, and $NR^cC(O)OR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c 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, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl,

C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from 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, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^g$, OR^g, SR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, NHR^g, NR^gR^g, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, and $NR^gC(O)OR^g$; wherein the 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, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^o$, $OC(O)NR^oR^o$, NHR^o, NR^oR^o, $NR^oC(O)R^o$, $NR^oC(O)NR^oR^o$, and $NR^oC(O)OR^o$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl of R^n is optionally substituted with 1, 2 or 3 R^q substituents;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, SR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, $OC(O)R^e$, $OC(O)NR^eR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, and $NR^eC(O)OR^e$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (5-10 membered heteroaryl)-C_{1-4} alkyl-; wherein the C_{1-6} alkyl and (5-10 membered heteroaryl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, and $NR^rC(O)R^r$;

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

each R^q is independently selected from OH, CN, -COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6

membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12} and $NR^{12}R^{12}$ and each R^{12} is independently C_{1-6} alkyl; and

----- is a single bond or a double bond to maintain ring A being aromatic.

32. The compound of claim **1**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, wherein the C_{1-4} alkyl and C_{1-4} alkoxy of R^1, R^2 and R^3 are each optionally substituted with 1 or 2 independently selected R^d substituents;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NO_2, OR^a, SR^a, $NHOR^a$, $C(O)R^a$, $C(O)NR^aR^a$, $C(O)OR^a$, NHR^a, NR^aR^a, and $NR^aC(O)R^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, NO_2, OR^{11}, SR^{11}, NH_2, $-NHR^{11}$, $-NR^{11}R^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $NR^{11}C(O)R^{11}$, and $NR^{11}C(O)OR^{11}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6}

haloalkoxy of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, phenyl substituted with 1-3 independently selected R^{b1} substituents, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^{11} 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^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

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

each R^b substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, $NHOR^c$, OR^c, $C(O)R^c$, $C(O)NR^cR^c$, and $C(O)OR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^b are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b1} is independently selected from Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_2, OR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, and $NR^cC(O)NR^cR^c$; wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy of R^{b1} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OH, NH_2, NO_2, $NHOR^c$, OR^c, SR^c, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, NHR^c, NR^cR^c, $NR^cC(O)R^c$, and $NR^cC(O)OR^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, (4-10 membered

heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, OR^g, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, NHR^g, NR^gR^g, and $NR^gC(O)R^g$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, phenyl, OR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, NHR^o, NR^oR^o, and $NR^oC(O)R^o$;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, $NHOR^e$, OR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, NHR^e, NR^eR^e, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, and $NR^eC(O)OR^e$, wherein the C_{1-6} alkyl and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (5-10 membered heteroaryl)-C_{1-4} alkyl-; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (5-10 membered heteroaryl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^r, $C(O)R^r$, $C(O)NR^rR^r$, and $C(O)OR^r$;

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

-----is a single bond or a double bond to maintain ring A being aromatic.

33. The compound of claim **1**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1 is CR^1;

X^2 is CR^2;

X^3 is CR^3;

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

X^5 is NR^5 or CR^5;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 5 independently selected R^6 substituents;

R^1, R^2 and R^3 are each independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OH, NH_2, -NH-C_{1-4} alkyl, and -N(C_{1-4} alkyl)$_2$;

R^4, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^a, $C(O)NR^aR^a$, and $NR^aC(O)R^a$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6}

alkynyl of R^4, R^5 and R^6 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two adjacent R^6 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^7 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or CN, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^7 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^8 is halo, C_{1-6} alkyl substituted with 1-3 independently selected R^{b2} substituents, C_{2-6} alkenyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{2-6} alkenyl and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^a is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 5-10 membered heteroaryl of R^a are each optionally substituted with 1, 2 or 3 independently selected R^d substituents;

each R^b substituent is independently selected from halo, C_{1-6} alkyl, and OR^c;

each R^{b2} is independently selected from halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, NHR^c, NR^cR^c, and $NR^cC(O)R^c$; wherein the C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl of R^{b2} are each further optionally substituted with 1-3 independently selected R^d substituents;

each R^c is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{6-10} aryl of R^c are each optionally substituted with 1, 2 or 3 R^f substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, OR^g, $C(O)R^g$, $C(O)NR^gR^g$, NHR^g, and NR^gR^g; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of

R^f are each optionally substituted with 1, 2 or 3 R^n substituents independently selected from C_{1-6} alkyl, halo, CN, OR^o, and $C(O)OR^o$;

each R^d is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NH_2, OR^e, $C(O)R^e$, $C(O)NR^eR^e$, $C(O)OR^e$, NHR^e, NR^eR^e, and $NR^eC(O)R^e$; wherein the C_{1-6} alkyl and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^d are each optionally substituted with 1-3 independently selected R^f substituents;

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

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

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

-----is a single bond or a double bond to maintain ring A being aromatic.

34. The compound of claim **1**, selected from:

(2S)-1-[(2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1,3-thiazol-5-yl)methyl]piperidine-2-carboxylic acid,

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide,

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-oxazole-2-carboxamide,

(2S)-1-[(1-methyl-2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1H-imidazol-5-yl)methyl]piperidine-2-carboxylic acid,

5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-N-(2-methylbiphenyl-3-yl)-1H-imidazole-2-carboxamide,

(2S)-1-[(1-methyl-3-{[(2-methylbiphenyl-3-yl)amino]carbonyl}-1H-pyrazol-5-yl)methyl]piperidine-2-carboxylic acid,

5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-N-(2-methylbiphenyl-3-yl)-1H-pyrazole-3-carboxamide,

4-chloro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide,

5-{[(2-hydroxyethyl)amino]methyl}-4-methyl-N-(2-methylbiphenyl-3-yl)-1,3-thiazole-2-carboxamide,

N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide,

N-(2-cyano-2'-fluorobiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide

N-(2-cyano-2'-fluoro-3'-methoxybiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide,

N-[2-cyano-3-(1-methyl-1H-indazol-4-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-pyrazole-3-carboxamide,

N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide,

N-(2-cyano-2'-fluoro-3'-methoxybiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide, and

N-[2-cyano-3-(1-methyl-1H-indazol-4-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}-1-methyl-1H-imidazole-2-carboxamide

or a pharmaceutically acceptable salt or a stereoisomer thereof.

35. The compound of claim **1**, selected from:

(S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-(((2-hydroxyethyl)amino)methyl)thiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid;

(S)-1-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)thiazole-2-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid; and

5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-N-(3'-(5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamido)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)thiazole-2-carboxamide;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

36. A pharmaceutical composition comprising a compound of any one of claims **1-35**, or a pharmaceutically acceptable salt or a stereoisomer thereof, and at least one pharmaceutically acceptable carrier or excipient.

37. A method of inhibiting PD-1/PD-L1 interaction, said method comprising administering to a patient a compound of any one of claims **1-35**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

38. A method of treating a disease or disorder associated with inhibition of PD-1/PD-L1 interaction, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims **1-35**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

39. A method of enhancing, stimulating and/or increasing the immune response in a patient, said method comprising administering to the patient in need thereof a therapeutically effective amount of a compound of any one of claims **1-35**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/048880

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D233/90 C07D403/06 C07D405/12 C07D417/06
C07D417/14 C07D263/34 C07D277/56
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 824 099 A1 (CARNA BIOSCIENCES INC [JP]) 14 January 2015 (2015-01-14) Formula (I); claims; compounds 72, 103, 108, 116 -----	1-6, 13-26, 30,33, 36,38,39
X	WO 2016/057500 A1 (MERCK PATENT GMBH [DE]; GAILLARD PASCALE [FR]; SEENISAMY JEYAPRAKASHNA) 14 April 2016 (2016-04-14) Formula (I); claims; compounds 43-45, 47-48 ----- -/--	1-6, 13-26, 30,33,36

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2017	02/11/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kirsch, Cécile

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/048880

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/080376 A1 (SYNGENTA PARTICIPATIONS AG [CH]; JUNG PIERRE JOSEPH MARCEL [CH]; HUETE) 21 June 2012 (2012-06-21) Formula (I); claims; compounds A92, A104, A150, A160, A162	1-6, 13-26, 30,33,36
X	WO 2006/053121 A2 (CGI PHARMACEUTICALS INC [US]; CURRIE KEVIN S [US]; KROPF JEFFREY E [US) 18 May 2006 (2006-05-18) Formula 1; page 95; claims	1-6, 13-26, 30,33, 36,38,39
X	WO 2011/082400 A2 (HARVARD COLLEGE [US]; SHARPE ARLENE H [US]; BUTTE MANISH J [US]; OYAMA) 7 July 2011 (2011-07-07) Formula (I); claims; examples	1-39

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/048880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2824099 A1	14-01-2015	CN 104169260 A	26-11-2014
		EP 2824099 A1	14-01-2015
		JP WO2013133367 A1	30-07-2015
		KR 20140131955 A	14-11-2014
		US 2015011751 A1	08-01-2015
		WO 2013133367 A1	12-09-2013
WO 2016057500 A1	14-04-2016	AR 102177 A1	08-02-2017
		AU 2015328285 A1	23-03-2017
		CA 2960401 A1	14-04-2016
		CN 107001362 A	01-08-2017
		EP 3204382 A1	16-08-2017
		KR 20170066566 A	14-06-2017
		PH 12017500408 A1	17-07-2017
		SG 11201701573Q A	30-03-2017
		US 2016096834 A1	07-04-2016
		WO 2016057500 A1	14-04-2016
WO 2012080376 A1	21-06-2012	AR 084308 A1	08-05-2013
		BR 112013014986 A2	12-07-2016
		CN 103261188 A	21-08-2013
		EP 2651921 A1	23-10-2013
		US 2013253011 A1	26-09-2013
		UY 33808 A	31-07-2012
		WO 2012080376 A1	21-06-2012
WO 2006053121 A2	18-05-2006	AU 2005304473 A1	18-05-2006
		BR PI0517619 A	14-10-2008
		CA 2587192 A1	18-05-2006
		CO 6382177 A2	15-02-2012
		EP 1812442 A2	01-08-2007
		JP 2008519843 A	12-06-2008
		KR 20070119606 A	20-12-2007
		NZ 555681 A	28-08-2009
		RU 2007121508 A	20-12-2008
		SG 159549 A1	30-03-2010
		US 2006178367 A1	10-08-2006
		WO 2006053121 A2	18-05-2006
WO 2011082400 A2	07-07-2011	US 2013022629 A1	24-01-2013
		WO 2011082400 A2	07-07-2011