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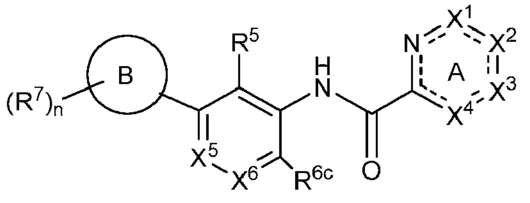
(54) Title: N-PHENYL-PYRIDINE-2-CARBOXAMIDE DERIVATIVES AND THEIR USE AS PD-1/PD-L1 PROTEIN/PROTEIN INTERACTION MODULATORS



(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.

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N-PHENYL-PYRIDINE-2-CARBOXAMIDE DERIVATIVES AND THEIR USE AS PD-1/PD-L1 PROTEIN/PROTEIN INTERACTION MODULATORS

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.

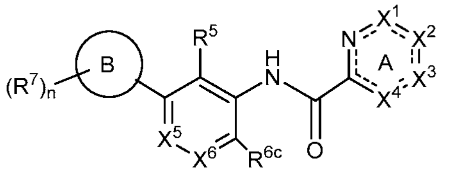
Programmed cell death-1 (PD-1), also known as CD279, is a cell surface receptor expressed on activated T cells, natural killer T cells, B cells, and macrophages (Greenwald et al, Annu. Rev. Immunol 2005, 23:515–548; Okazaki and Honjo, Trends Immunol 2006, (4):195-201). It functions as an intrinsic negative 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

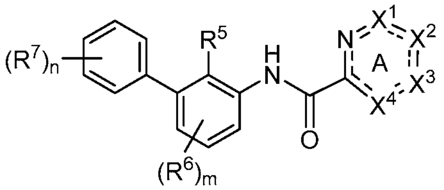
The present disclosure provides, *inter alia*, a compound of Formula (I'):



(I')

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

The present disclosure further provides, *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.

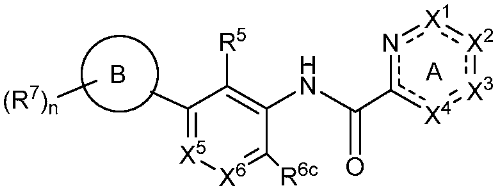
The present disclosure further provides methods of modulating or inhibiting PD-1/PD-L1 protein/protein interaction, which comprises administering to an individual a compound of the disclosure, or a pharmaceutically acceptable salt or a stereoisomer thereof.

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

The present disclosure provides compounds 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is N or CR^{6b};

ring B is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, provided ring B is other than 9-H-carbazol-4-yl, 2,3,4,9-tetrahydro-1H-carbazol-5-yl or 1H-tetrazolyl;

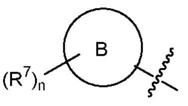
R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} 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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 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, $-NHR^{11}$, $-NR^{11}R^{11}$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, and $S(O)_2NR^{11}R^{11}$, 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^5 are each optionally substituted with 1, 2 or 3 R^b substituents; wherein R^5 is other than F when ring B is C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl or 4- to 10-membered heterocycloalkyl;

each R^{11} is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 R^b substituents;

R^{6a}, R^{6b} and R^{6c} 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_{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- of R^{6a}, R^{6b}, R^{6c} and R^{10} are each optionally substituted with 1, 2 or 3 independently selected R^d substituents;

or two adjacent R^7 substituents, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 4- to 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 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- to 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-10} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents, provided  is other than 9-H-carbazol-4-yl or 2,3,4,9-tetrahydro-1H-carbazol-5-yl, each of which is optionally substituted by 1, 2 or 3 independently selected R^b substituents;

or two R^7 substituents attached to the same ring carbon atom of ring B, together with the carbon atom to which they are attached, form a 4- to 7-membered heterocycloalkyl ring having 1-4 heteroatoms as ring members selected from N, O and S or a C_{3-6} cycloalkyl ring, wherein the 4- to 7-membered heterocycloalkyl ring and C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^1 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^2 and X^1 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^2 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^3 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^3 and X^4 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^4 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d 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^b substituent is independently selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} 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, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, 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_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} 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^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 3, 4, or 5 R^n substituents independently selected from C_{1-4} alkyl, 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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, halo, CN, R^o, $NHOR^o$, 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_{1-4} alkyl, 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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-4} haloalkyl of R^n are each optionally substituted with 1, 2 or 3 R^q substituents;

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} 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_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} 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 are each 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_{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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 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, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{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 further optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}haloalkoxy, CN, NHOR^k, OR^k, SR^k, C(O)R^k, C(O)NR^{k}R^k, C(O)OR^k, OC(O)R^k, OC(O)NR^{k}R^k, NHR^k, NR^{k}R^k, NR^{k}C(O)R^k, NR^{k}C(O)NR^{k}R^k, NR^{k}C(O)OR^k, C(=NR^k)NR^{k}R^k, NR^{k}C(=NR^k)NR^{k}R^k, S(O)R^k, S(O)NR^{k}R^k, S(O)$_2$R^k, NR^{k}S(O)$_2$R^k, NR^{k}S(O)$_2$NR^{k}R^k, and S(O)$_2$NR^{k}R^k, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-6} alkynyl, 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; and

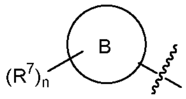
each R^e, R^i, R^k, R^o or R^r is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{1-4} haloalkyl, C_{2-4}

alkenyl, and C_{2-4} alkynyl, 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, and C_{2-4} alkynyl of R^e, 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} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^8, NR^8R^8, and C_{1-4} haloalkoxy, 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, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl and each R^8 is independently C_{1-6} alkyl;

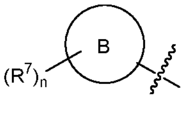
⎓ is a single bond or a double bond, wherein ring A includes at least one double bond;

the subscript n is an integer of 1, 2, 3, 4 or 5; and

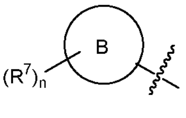
with the proviso (i) when  is 2,6-dioxohexahydropyrimidin-1-yl, 2-oxopyrrolidin-1-yl, benzo[d]thiazol-2-yl, 2-amino-4-methyl-5,6-dihydro-1,3-thiazin-4-yl, 4-methyl-6-[4-(morpholine-4-carbonyl)anilino]-5-oxo-pyrazin-2-yl, 5,7-dimethylbenzo[d]oxazol-2-yl, 6-[4-(morpholine-4-carbonyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl, 8-[4-(morpholine-4-carbonyl)anilino]imidazo[1,2-a]pyrazin-6-yl, oxazolo[4,5-b]pyridine-2-yl, or 1-methyl-2-oxo-1,6-naphthridin-3-yl, ring A in Formula (I') is not 2-pyridyl or 2-pyridyl optionally substituted with halo, methylcarboxy, 1,2,4-triazol-4-yl, 1-piperidinyl, or cyclopropyl;

(ii) when ring B is thiazolo[5,4-b]pyridin-2-yl or 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl, ring A in Formula (I') is other than 2-quinolyl;

(iii) when ring B is 1-piperazinyl, ring A in Formula (I') is not 3-(4-benzyloxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl;

(iv) when  is 6-[1-(dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-4-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl, ring A in Formula (I') is not 1-methylpyrrolo[2,3-b]pyridine-6-yl;

(v) when ring B is 2-oxo-1,2-dihydropyridin-5-yl, 2-oxo-1,2-dihydropyrazin-5-yl or 6-oxo-1H-pyridazin-3-yl, R^2 is other than t-butyl;

(vi) when 

is 3,5-dimethylphenyl, R^5 is other than 4-amino-1-piperidinyl; and

(vii) the compound is other than 6-((2R,6S)-2,6-dimethylmorpholino)-N-(2-methyl-4'-(trifluoromethoxy)biphenyl-3-yl)pyridazine-3-carboxamide or N-(3-(3-acetyl-2-oxoimidazolidin-1-yl)-2-methylphenyl)-5,6,7,8-tetrahydroquinoline-2-carboxamide.

The present disclosure provides componds 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is N or CR^{6b};

Ring B is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, provided ring B is other than 9-H-carbazol-4-yl, 2,3,4,9-tetrahydro-1H-carbazol-5-yl or 1H-tetrazolyl;

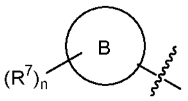
R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} 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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 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, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, and $S(O)_2NR^{11}R^{11}$, 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^5 are each optionally substituted with 1, 2 or 3 R^b substituents; wherein R^5 is other than F when ring B is C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl or 4- to 10-membered heterocycloalkyl;

each R^{11} is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 R^b substituents;

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

or two adjacent R^7 substituents, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 4- to 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 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- to 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-10} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents, provided 

is other than 9-H-carbazol-4-yl or 2,3,4,9-tetrahydro-1H-carbazol-5-yl, each of which is optionally substituted by 1 or 2 independently selected R^b substituents;

or two R^7 substituents attached to the same ring carbon atom of ring B, together with the carbon atom to which they are attached, form a 4- to 7-membered heterocycloalkyl ring having 1-4 heteroatoms as ring members selected from N, O and S or a C_{3-6} cycloalkyl ring, wherein the 4- to 7-membered heterocycloalkyl ring and C_{3-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^1 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^1 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^3 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^3 and X^4 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^4 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, 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, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-4} alkyl, C_{3-10} cycloalkyl and

4-10 membered heterocycloalkyl of R^d are each further optionally substituted with 1-3 independently selected R^f substituents;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, 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_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 3, 4, or 5 R^n substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, R^o, $NHOR^o$, 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 $S(O)_2NR^oR^o$;

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 independently selected R^p 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_{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_{1-6} haloalkyl, 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, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{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-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each further optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, 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 $S(O)_2NR^kR^k$; 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;

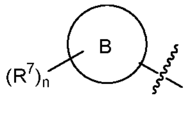
or any two R^k substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

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; and

each R^e, R^i, R^k, R^o or R^p is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 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_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, and C_{2-4} alkynyl of R^e, R^i, R^k, R^o or R^p 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} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^8, NR^8R^8, and C_{1-4} haloalkoxy, 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} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^8 is independently C_{1-6} alkyl;

⎓ is a single bond or a double bond, wherein ring A includes at least one double bond;the subscript n is an integer of 1, 2, 3, 4 or 5; and

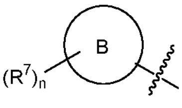
with the proviso (i) when 

is 2,6-dioxohexahydropyrimidin-1-yl, 2-oxopyrrolidin-1-yl, benzo[d]thiazol-2-yl, 2-amino-4-methyl-5,6-dihydro-1,3-thiazin-4-yl, 4-methyl-6-[4-(morpholine-4-carbonyl)anilino]-5-oxo-pyrazin-2-yl, 5,7-dimethylbenzo[d]oxazol-2-yl, 6-[4-(morpholine-4-carbonyl)phenyl]-7H-pyrrolo[2,3-

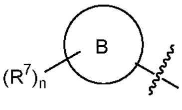
d]pyrimidin-4-yl, 8-[4-(morpholine-4-carbonyl)anilino]imidazo[1,2-a]pyrazin-6-yl, oxazolo[4,5-b]pyridine-2-yl, or 1-methyl-2-oxo-1,6-naphthridin-3-yl, ring A in Formula (I’) is not 2-pyridyl or 2-pyridyl optionally substituted with halo, methylcarboxy, 1,2,4-triazol-4-yl, 1-piperidinyl, or cyclopropyl;

(ii) when ring B is thiazolo[5,4-b]pyridin-2-yl or 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl, ring A in Formula (I’) is other than 2-quinolyl;

(iii) when ring B is 1-piperazinyl, ring A in Formula (I’) is not 3-(4-benzyloxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl;

(iv) when  is 6-[1-(dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-4-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl, ring A in Formula (I’) is not 1-methylpyrrolo[2,3-b]pyridine-6-yl;

(v) when ring B is 2-oxo-1,2-dihydropyridin-5-yl, 2-oxo-1,2-dihydropyrazin-5-yl or 6-oxo-1H-pyridazin-3-yl, R^2 is other than t-butyl;

(vi) when  is 3,5-dimethylphenyl, R^5 is other than 4-amino-1-piperidinyl; and

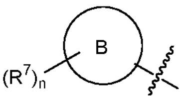
(vii) the compound is other than 6-((2R,6S)-2,6-dimethylmorpholino)-N-(2-methyl-4'-(trifluoromethoxy)biphenyl-3-yl)pyridazine-3-carboxamide or N-(3-(3-acetyl-2-oxoimidazolidin-1-yl)-2-methylphenyl)-5,6,7,8-tetrahydroquinoline-2-carboxamide.

In some embodiments, when Cy is 2-oxo-1,2-dihydropyridin-5-yl, 2-oxo-1, 2-dihydropyrazin-5-yl or 6-oxo-1,5-dihydropyridazin-3-yl, each of which is optionally substituted, R^2 is other than C_{1-6} alkyl.

In some embodiments of compounds of Formula (I’), R^5 is C_{1-4} alkyl, halo, CN, OH, cyclopropyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $-NH-C_{1-4}$ alkyl, $-N(C_{1-4}\text{ alkyl})_2$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, and $S(O)_2NR^{11}R^{11}$, wherein C_{1-4} alkyl, cyclopropyl, C_{2-4} alkynyl and C_{1-4} alkoxy of R^5 are each optionally substituted with 1 or 2 halo, OH, CN or OCH_3 substituent and each R^{11} is independently selected from H and C_{1-4} alkyl optionally substituted with 1 or 2 halo, OH, CN or OCH_3; wherein R^5 is other than F when ring B is C_3-

$_{10}$ cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl. In some embodiments of compounds of Formula (I'), ring A is aromatic.

In some embodiments of compounds of Formula (I'), ring B is C_{6-10} aryl. In certain embodiments, ring B is phenyl or naphthyl. In certain embodiments, ring B is phenyl. R^7 is as defined in any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments, each R^7 is H.

In some embodiments, ring B is 1-cyclohexenyl, cyclohexyl, 3,4-dihydro-2H-pyridin-5-yl, 1,2,3,4-tetrahydropyridin-5-yl, 1-piperidinyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 3,4-dihydro-2H-pyran-5-yl, 4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl, 3,4-dihydro-2H-1,4-benzoxazin-7-yl, 2,3-dihydro-1-benzofuran-6-yl, 2-methyl-2H-indazol-6-yl, 2H-indazol-6-yl, 1-methyl-1H-indazol-4-yl or 1H-indazol-4-yl. R^7 is as defined in any embodiment of compounds of Formula (I') or Formula (I) as described herein. In some embodiments, R^7 is t-butoxycarbonyl or C_{1-6} alkyl. In certain embodiments,  is 1-cyclohexenyl, cyclohexyl, 1-t-butoxycarbonyl-3,4-dihydro-2H-pyridin-5-yl, 1,2,3,4-tetrahydropyridin-5-yl, 1-piperidinyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 3,4-dihydro-2H-pyran-5-yl, 4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl, 3,4-dihydro-2H-1,4-benzoxazin-7-yl, 2,3-dihydro-1-benzofuran-6-yl, 2-methyl-2H-indazol-6-yl, 2H-indazol-6-yl, 1-methyl-1H-indazol-4-yl or 1H-indazol-4-yl.

In some embodiments of compounds of Formula (I'), ring B is C_{3-10} cycloalkyl. In certain embodiments, ring B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl or cyclooctyl. R^7 is as defined in any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments, R^7 is H.

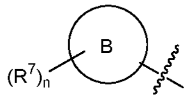
In some embodiments of compounds of Formula (I'), ring B is 5- to 14-membered heteroaryl. In certain embodiments, ring B is pyridy, primidinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furanyl, thiophenyl, quinolinyl, isoquinolinyl, naphthyridinyl, indolyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1,2-*b*]thiazolyl, purinyl, 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. In certain embodiments, ring B is 2-methyl-2H-indazol-6-yl, 1-methyl-1H-indazol-4-yl, 2,3-dihydro-1-benzofuran-6-yl, 4-

methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl or 2,3-dihydro-1,4-benzodioxin-6-yl. R^7 is as defined in any embodiment of compounds of Formula (I') or Formula (I) as described herein.

In some embodiments of compounds of Formula (I'), ring B is 4- to 10-membered heterocycloalkyl. In certain embodiments, ring B is 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, 2,3-dihydro-1,4-benzodioxin-6-yl, or thiomorpholino. In some embodiments, ring B is 3,4-dihydro-2H-pyran-5-yl, 1-piperidinyl or 1,2,3,4-tetrahydropyridin-5-yl. R^7 is as defined in any embodiment of compounds of Formula (I') or Formula (I) as described herein.

In some embodiments of compounds of Formula (I'), ring B is phenyl, 5- or 6-membered heteroaryl, C_{3-6} cycloalkyl or 5- or 6-membered heterocycloalkyl. In certain instances, ring B is phenyl, 2-thiophenyl, 3-thiophenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_{3-6} cycloalkyl or 3,6-dihydro-2H-pyran-4-yl. R^7 is as defined in any embodiment of compounds of Formula (I') or Formula (I) as described herein.

In some embodiments of compounds of Formula (I'), X^5 and X^6 are each CH. In certain embodiments, X^5 is N and X^6 is CH. In certain embodiments, X^5 is CH and X^6 is N. In certain embodiments, X^5 and X^6 are each N.

In some embodiments of compounds of Formula (I'), when 

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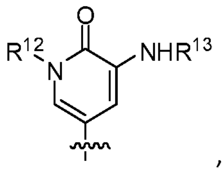

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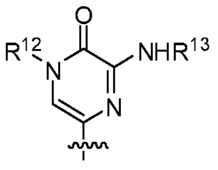

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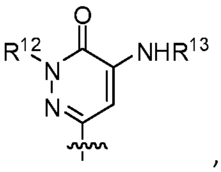
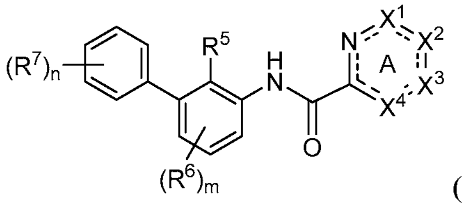


, R^2 is other than t-butyl or C_{1-6} alkyl, wherein each R^{12} is independently H or CH_3 and each R^{13} is independently phenyl substituted with amino and morpholino, phenyl substituted with a group selected from R^{14}, -C(O)R^{14} and (2-amino-2-oxo-ethyl)methylcarbamoyl, 2-pyridyl substituted with 4-methylpiperazin-1-yl or 1-methylpyrrolidin-2-yl , 3-pyridizinyl substituted with morpholino or 4-methylpiperazin-1-yl , 5-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-2-yl, 5-trideuteriomethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-2-yl, 5-(2,2-difluoroethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-2-yl, 1-methylpyrazol-3-yl, 4-pyrimidinyl, wherein R^{14} is selected from morpholino, 4-ethylpiperazin-1-yl, 1,1-dioxo-1,4-thiazinan-4-yl, 4-oxo-1-piperidinyl, 4-methyl-1-piperidinyl, 4-oxo-piperidin-1-yl, 2-(hydroxymethyl)morpholin-4-yl.

In some embodiments, the present disclosure provides componds 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

R^1, R^2, R^3, R^4 and R^7 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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 is C_{1-4} alkyl, halo, CN, OH, cyclopropyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, and $S(O)_2NR^{11}R^{11}$, wherein each R^{11} is independently selected from H and C_{1-4} alkyl optionally substituted with 1 or 2 halo, OH, CN or OCH_3;

each R^6 is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, 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 H or C_{1-4} alkyl optionally substituted with 1 or 2 groups independently selected from halo, OH, CN and C_{1-4} alkoxy, and wherein the C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{2-4} alkenyl and C_{2-4} alkynyl of R^6 are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN, C_{1-4} alkyl and C_{1-4} alkoxy;

or two adjacent R^7 substituents, taken together with the carbon atoms to which they are attached, form a fused phenyl ring, a fused 5- to 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{5-6} cycloalkyl ring, wherein the fused 5- to 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- to 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-10} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^q substituents;

or R^1 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^1 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-

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

or R^3 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^3 and X^4 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^4 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

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

$NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-4} alkyl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl of R^d are each further optionally substituted with 1-3 independently selected R^q substituents or 1-3 independently selected R^f substituents;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, 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_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 3, 4, or 5 R^n substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, R^o, $NHOR^o$, 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 $S(O)_2NR^oR^o$;

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 independently selected R^p 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_{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_{1-6} haloalkyl, 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, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{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-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each further optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, 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 $S(O)_2NR^kR^k$; 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; and

each R^e, R^i, R^k, R^o or R^p is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 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_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, and C_{2-4} alkynyl of R^e, R^i, R^k, R^o or R^p 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_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, NHR^8, NR^8R^8, and C_{1-4} haloalkoxy, wherein the C_{1-4} alkyl, phenyl and 5-6 membered heteroaryl of R^q are each optionally substituted with OH, CN, -COOH, NH_2, C_{1-4} alkoxy, C_{3-10} cycloalkyl and 4-, 5-, or 6-membered heterocycloalkyl and each R^8 is independently C_{1-6} alkyl;

the subscript n is an integer of 1, 2, 3, 4 or 5;

the subscript m is an integer of 1, 2, 3 or 4; and

$\overline{\cdots\cdots}$ is a single bond or a double bond, wherein ring A includes at least one double bond;

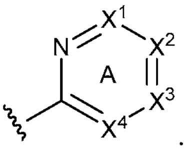
with the proviso that the compound is other than 6-((2R,6S)-2,6-dimethylmorpholino)-N-(2-methyl-4'-(trifluoromethoxy)biphenyl-3-yl)pyridazine-3-carboxamide. In some embodiments of compounds of Formula (I), the subscript m is an integer of 1, 2 or 3. The compounds, or pharmaceutically acceptable salts or stereoisomers thereof, as described herein are useful as inhibitors of the PD-1/PD-L1 protein/protein interaction. For example, compounds or pharmaceutically acceptable salts or stereoisomers thereof as described herein can disrupt the PD-1/PD-L1 protein/protein interaction in the PD-1 pathway.

In some embodiments of compounds of Formula (I), R^5 is 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, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, and $S(O)_2NR^{11}R^{11}$, 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^5 are each optionally substituted with 1, 2 or 3 R^b substituents; wherein R^5 is other than F when Cy is C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl;

each R^{11} is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 R^b substituents.

In some embodiments, ring A is other than pyridazinyl group. In some instances, when X^2 is CR^2, X^3 is CR^3 and X^4 is CR^4, X^1 is other than N.

In some embodiments, ring A is aromatic.

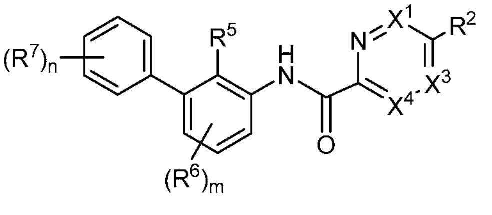
In some embodiments, ring A has the formula:  .

In some embodiments, R^1 and R^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents.

In some embodiments, R^2 and R^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents.

In some embodiments, R^3 and R^4 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents.

In some embodiments, the present disclosure provides compounds having Formula (II):

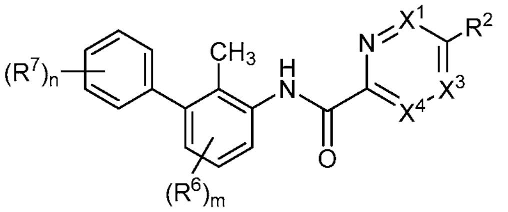


(II)

or a pharmaceutically acceptable salt or a stereoisomer thereof. In certain embodiments of compounds of Formula (II), R^2 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^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,

$NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^2 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof. Other variables of Formula (II) are as defined in Formula (I'), Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein. In one embodiment of compounds of Formula (II), R^5 is CN or C_{1-4} alkyl optionally substituted with R^q. In another embodiment, R^5 is CH_3 or CN.

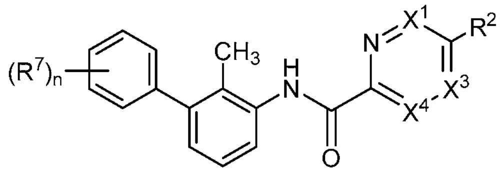
In some embodiments, the present disclosure provides compounds having Formula (III):



(III)

or a pharmaceutically acceptable salt or a stereoisomer thereof. In certain embodiments of compounds of Formula (III), R^2 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^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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^2 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof. Other variables of Formula (III) are as defined in Formula (I'), Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein.

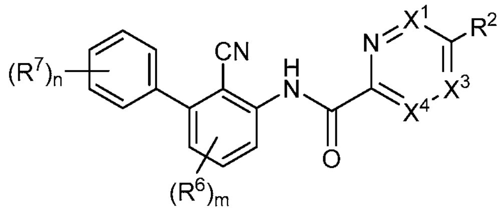
In some embodiments, the present disclosure provides compounds having Formula (IV):



(IV)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (IV) are as defined in Formula (I'), Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments of compounds of Formula (II), R^2 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^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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^2 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof.

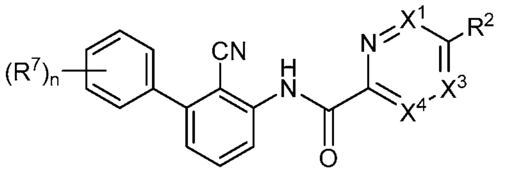
In some embodiments, the present disclosure provides compounds having Formula (V):



(V)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (V) are as defined in Formula (I'), Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments of compounds of Formula (V), R^2 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^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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^2 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof.

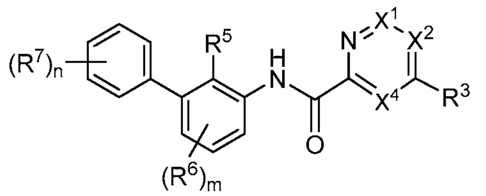
In some embodiments, the present disclosure provides compounds having Formula (VI):



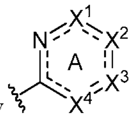
(VI)

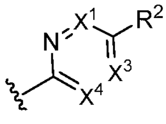
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (VI) are as defined in Formula (I'), Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments of compounds of Formula (VI), R^2 is halo, C_{1-6} 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^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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^2 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof.

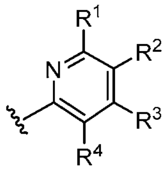
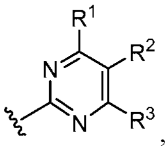
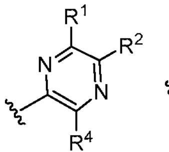
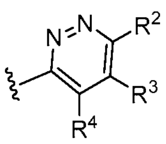
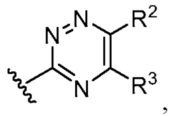
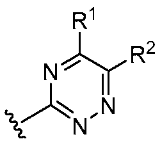
In some embodiments, the present disclosure provides compounds having Formula (VII):

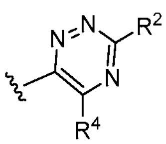

(VII)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (VII) are as defined in Formula (I'), Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments of compounds of Formula (VII), R^3 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^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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^2 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof.

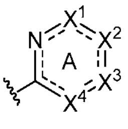
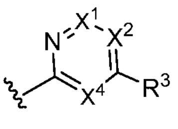
In some embodiments of compounds of Formula I', I, II, III, IV, V or VI, or a pharmaceutically acceptable salt or a stereoisomer thereof, the moiety  or

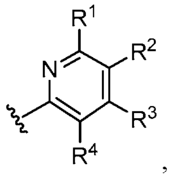
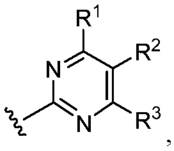
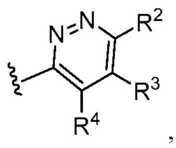
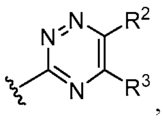
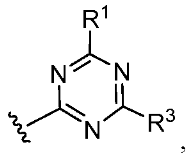
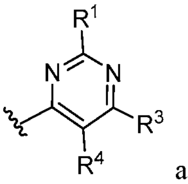
 is selected from:

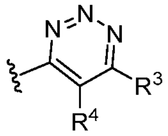
 ,  ,  ,  ,  ,  and

 , wherein the substituents R^1, R^2, R^3 and R^4 are as defined in Formula (I'),

Formula (I') or Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments, at each occurrence, R^1, R^3 and R^4 are each H.

In some embodiments of compounds of Formula I', I or VII, or a pharmaceutically acceptable salt or a stereoisomer thereof, the moiety the moiety  or  is selected from:

, , , , ,  and

, wherein the substituents R^1, R^2, R^3 and R^4 are as defined in Formula (I'), Formula (I) or any embodiment of compounds of Formula (I') or Formula (I) as described herein. In certain embodiments, at each occurrence, R^1, R^2 and R^4 are each H.

In some embodiments of compounds of Formula I', I, II, III, IV, V or VI, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is CR^1, X^3 is CR^3 and X^4 is CR^4.

In some embodiments of compounds of Formula I', I, II, III, IV, V or VI, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is CR^1, X^3 is CR^3 and X^4 is N.

In some embodiments of compounds of Formula I', I, II, III, IV, V or VI, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is CR^1, X^3 is N and X^4 is CR^4.

In some embodiments of compounds of Formula I', I, II, III, IV, V or VI, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is N, X^3 is CR^3 and X^4 is CR^4.

In some embodiments of compounds of Formula I', I or VII, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is CR^1, X^2 is CR^2 and X^4 is CR^4.

In some embodiments of compounds of Formula I', I or VII, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is CR^1, X^2 is CR^2 and X^4 is N.

In some embodiments of compounds of Formula I', I or VII, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is CR^1, X^2 is N and X^4 is CR^4.

In some embodiments of compounds of Formula I', I or VII, or a pharmaceutically acceptable salt or a stereoisomer thereof, X^1 is N, X^2 is CR^2 and X^4 is CR^4.

In some embodiments, R^1, R^3 and R^4, are each independently selected from H, C_{1-6} alkyl, CN, -N(C_{1-6} alkyl)$_2$ and halo.

In some embodiments, R^1, R^2 and R^4, are each independently selected from H, C_{1-6} alkyl, CN, -N(C_{1-6} alkyl)$_2$ and halo.

In some embodiments, R^1, R^2, R^3, R^4, R^6 and R^7 are each H.

In some embodiments, R^1, R^3, R^4, R^6 and R^7 are each H.

In some embodiments, R^1, R^2, R^4, R^6 and R^7 are each H.

In some embodiments, two adjacent R^7 substituents on the phenyl ring taken together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered fused heterocycloalkyl optionally substituted by 1 or 2 R^q substituents. In certain instances, the fused heterocycloalkyl has carbon and 1 or 2 heteroatoms as ring members selected from O, N or S, wherein the carbon ring atom is optionally oxidized to form carbonyl, the N ring atom is optionally oxidized to form NO and the S ring atom is optionally oxidized to form SO or SO_2.

In some embodiments, the subscript n is 2 and the subscript m is 1.

In some embodiments, R^5 is C_{1-4} alkyl or CN.

In some embodiments, R^5 is CH_3 or CN.

In some embodiments, R^6 and R^7 are each H.

In some embodiments of compounds of Formula I', I, II, III, III, IV, V or VI, R^2 is C_{1-4} alkyl substituted with R^b. In certain embodiments, R^b is NHR^c or NR^cR^c. In certain embodiments, R^b is NR^cR^c. In other embodiments, R^b is 2-hydroxyethylamino, 2-hydroxyethyl(methyl)amino, 2-carboxypiperidin-1-yl, (cyanomethyl)amino, (S)-2-carboxypiperidin-1-yl, (R)-2-carboxypiperidin-1-yl or 2-carboxypiperidin-1-yl, each of which is optionally substituted with 1, 2 or 3 R^q substituents. In other embodiments, R^2 is C_{1-4} alkyl substituted with R^q.

In some embodiments of compounds of Formula I', I, II, III, III, IV, V or VI, R^2 is C_{1-4} alkoxy substituted with R^d. In certain embodiments, R^d is phenyl, 3-cyanophenyl, 3-pyridyl, 2-pyridyl, or 4-pyridyl, each of which is optionally substituted with 1, 2 or 3 R^q substituents.

In some embodiments of compounds of Formula I', I, II, III, III, IV, V or VI, R^2 is $-OCH_2R^d$. In certain embodiments, R^d is phenyl, 3-cyanophenyl, 3-pyridyl, 2-pyridyl, 4-pyridyl, each of which is optionally substituted with 1, 2 or 3 R^q substituents.

In some embodiments, when X^1 is N, X^3 is CH and X^4 is CH, R^2 is other than cis-2,6-dimethylmorpholino. In other embodiments, X^1 is N, X^3 is CH and X^4 is CH, R^2 is other than 2,6-dimethylmorpholino. In other embodiments, X^1 is N, X^3 is CH and X^4 is CH, R^2 is other than 6-membered heterocycloalkyl substituted with 1 or 2 C_{1-6} alkyl, wherein the heterocycloalkyl has N and O as ring members. In other embodiments, ring A is other than 6-(2,6-dimethylmorpholino)pyridazin-3-yl.

In some embodiments of compounds of Formula I', I or VII, R^3 is C_{1-4} alkyl substituted with R^b. In certain embodiments, R^b is NHR^c or NR^cR^c. In other embodiments, R^b is 2-hydroxyethylamino, 2-hydroxyethyl(methyl)amino, 2-carboxypiperidin-1-yl, (cyanomethyl)amino, (S)-2-carboxypiperidin-1-yl, (R)-2-carboxypiperidin-1-yl or 2-carboxypiperidin-1-yl, each of which is optionally substituted with 1, 2 or 3 R^q substituents. In other embodiments, R^3 is C_{1-4} alkyl substituted with R^q.

In some embodiments of compounds of Formula I', I or VII, R^3 is C_{1-4} alkoxy substituted with R^d. In certain embodiments, R^d is phenyl, 3-cyanophenyl, 3-pyridyl, 2-pyridyl, or 4-pyridyl, each of which is optionally substituted with 1, 2 or 3 R^q substituents.

In some embodiments of compounds of Formula I', I or VII, R^3 is $-OCH_2R^d$. In certain embodiments, R^d is phenyl, 3-cyanophenyl, 3-pyridyl, 2-pyridyl, 4-pyridyl, each of which is optionally substituted with 1, 2 or 3 R^q substituents.

In some embodiments of compounds of Formula I', I, II, III, IV, V or VI, R^3 is 2-hydroxyethylaminomethyl, 2-hydroxyethyl(methyl)aminomethyl, 2-carboxypiperidin-1-ylmethyl, (cyanomethyl)aminomethyl, (S)-2-carboxypiperidin-1-ylmethyl, (R)-2-carboxypiperidin-1-ylmethyl, 2-carboxypiperidin-1-ylmethyl, benzyloxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-pyridylmethoxy, 3-pyridylmethoxy, or 4-pyridylmethoxy, each of which is optionally substituted with 1, 2 or 3 R^q substituents. In certain embodiments, R^3 is 2-hydroxyethylaminomethyl, 2-carboxypiperidin-1-ylmethyl, (S)-2-carboxypiperidin-1-ylmethyl, (R)-2-carboxypiperidin-1-ylmethyl or (3-cyanobenzyl)oxy, each of which is optionally substituted with 1, 2 or 3 R^q substituents.

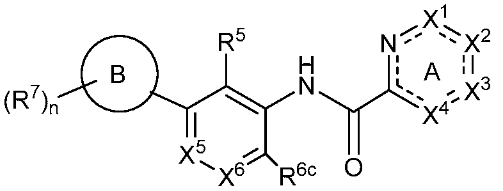
In some embodiments of compounds of Formula I', R^{6a}, R^{6b} and R^{6c} are each independently selected from H, halo, CN, $N(C_{1-6}$ alkyl$)_2$, C_{1-6} alkyl and C_{1-6} alkoxy, wherein the C_{1-6} alkyl are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN, C_{1-4} alkyl and C_{1-4} alkoxy.

In some embodiments of compounds of Formula I', R^{6a}, R^{6b} and R^{6c} are each independently selected from H, halo, CN, $N(CH_3)_2$ and CH_3.

In some embodiments of compounds of Formula I, II, III, V, or VII, R^6 is H, halo, CN, $N(C_{1-6}$ alkyl$)_2$, C_{1-6} alkyl or C_{1-6} alkoxy, wherein the C_{1-6} alkyl and C_{1-6} alkoxy are each optionally substituted with 1-3 R^q substituents.

In some embodiments of compounds of Formula I, II, III, V or VIII, R^6 is H, halo, CN, $N(CH_3)_2$ or CH_3.

In some embodiments, 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is CR^{6b};

ring B is phenyl, cyclohexyl, piperidinyl, or tetrahydropyridinyl;

R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, 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, OR^a, NHR^a, and NR^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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or CN, 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^5 are each optionally substituted with 1, 2 or 3 R^b substituents;

R^{6a}, R^{6b} and R^{6c} 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, NH_2, $-NH-C_{1-4}$ alkyl, and $-N(C_{1-4}\text{ alkyl})_2$, wherein the C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl of R^{6a}, R^{6b}, and R^{6c} are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN, C_{1-4} alkyl and C_{1-4} alkoxy;

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

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, CN, NH_2, 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, and $NR^eC(O)R^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-4} alkyl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl of R^d are each further optionally substituted with 1-3 independently selected R^f substituents;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, 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_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^b 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_{1-4} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 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, and $NR^gC(O)R^g$;

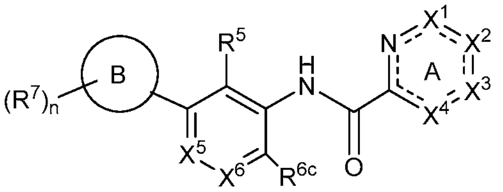
each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

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

$\overset{---}{---}$ is a single bond or a double bond, wherein ring A includes at least one double bond; and

the subscript n is an integer of 1, 2, 3, 4 or 5.

In some embodiments, 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is CR^{6b};

ring B is phenyl, cyclohexyl, piperidinyl, or tetrahydropyridinyl;

R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OR^a, NHR^a, and NR^aR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 is C_{1-6} alkyl or CN;

R^{6a}, R^{6b} and R^{6c} 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)$_2$;

or two adjacent R^7 substituents, taken together with the atoms to which they are attached, form a fused 4- to 7-membered heterocycloalkyl ring or a fused 5- or 6-membered heteroaryl ring, wherein the fused 4- to 7-membered heterocycloalkyl ring and fused 5- or 6-

membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N and O and wherein the fused 5- to 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, and NH_2;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, OH, NH_2, $C(O)OR^c$, NHR^c, and NR^cR^c;

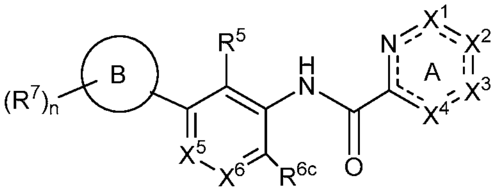
each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4}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

$\overset{---}{---}$ is a single bond or a double bond, wherein ring A includes at least one double bond; and

the subscript n is an integer of 1, 2, 3, 4 or 5.

In some embodiments, 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is CR^{6b};

ring B is phenyl, cyclohexyl, piperidinyl, or tetrahydropyridinyl;

R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OR^a, NHR^a, and NR^aR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1 or 2, R^b substituents;

R^5 is C_{1-6} alkyl or CN;

R^{6a}, R^{6b} and R^{6c} are each independently selected from H, C_{1-4} alkyl and halo;

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

each R^a is independently selected from H, CN, 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-, 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^a are each optionally substituted with 1 or 2 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, halo, CN, and NH_2;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, CN, OH, NH_2, $C(O)OR^c$, NHR^c, and NR^cR^c;

each R^c is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^c are each optionally substituted with 1, 2 or R^f substituents independently selected from C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, and OR^g;

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

⎓ is a single bond or a double bond, wherein ring A includes at least one double bond; and

the subscript n is an integer of 1, 2, 3, 4 or 5.

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') or 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," employed alone or in combination with other terms, refers to a group of formula $–NH_2$.

The term "carbamyl," employed alone or in combination with other terms, refers to a group of formula $–C(O)NH_2$.

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," employed alone or in combination with other terms, 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," employed alone or in combination with other terms, 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 carbon atoms. In some embodiments aryl groups have 6 carbon atoms. In some embodiments aryl groups have 10 carbon atoms. In some embodiments, the aryl group is phenyl. In some embodiments, the aryl group is naphthyl.

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 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, 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.

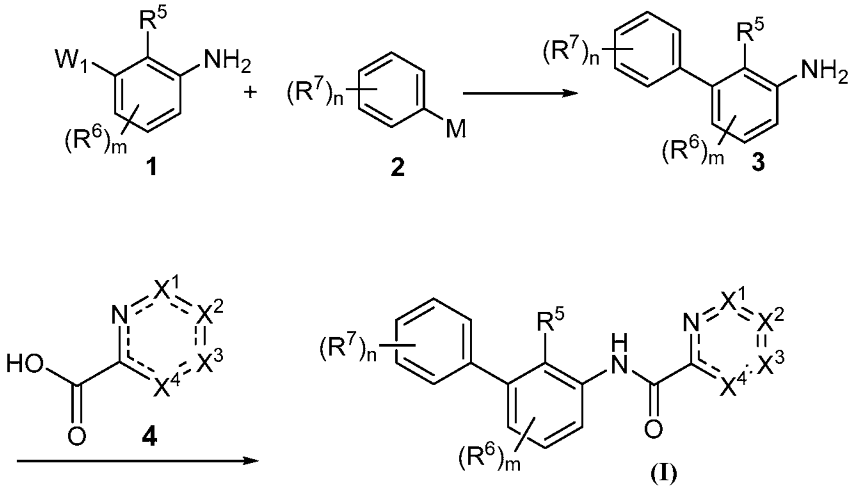
The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the 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); Petursson *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).

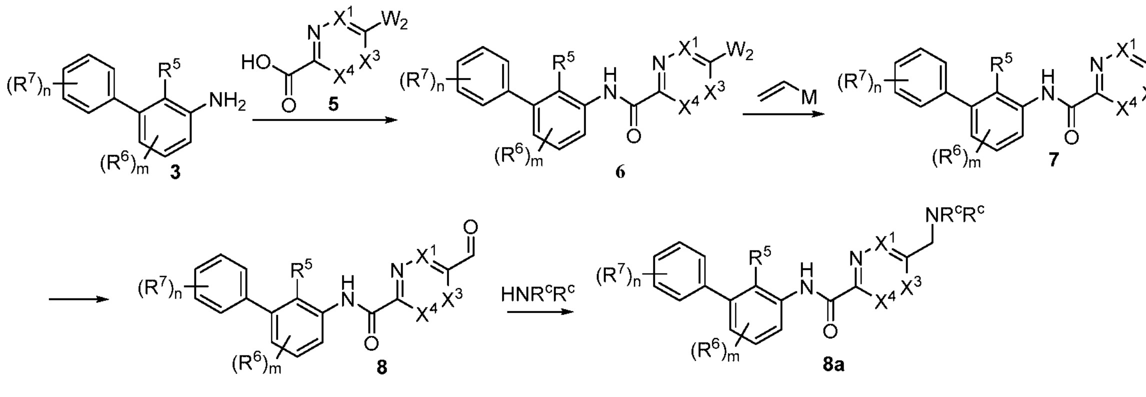
The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

Compounds of Formula (I') and Formula (I) can be synthesized using a process shown in Scheme 1. In Scheme 1, a suitable halo (W_1)-substituted aromatic amine **1** is reacted with a suitable coupling reagent **2** (where M is, *e.g.*, $-B(OH)_2$) to produce compound **3** under standard metal catalyzed cross-coupling reaction conditions (such as Suzuki coupling reaction, *e.g.*, in the presence of a palladium catalyst (*e.g.*, 1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)) and a base (*e.g.*, a bicarbonate or a carbonate base)). Then the aromatic amine **3** is reacted with an acid of formula **4** under suitable conditions forming an amide bond to provide the product of formula (I) using coupling reagents such as, but not limited to, HATU and DIPEA.



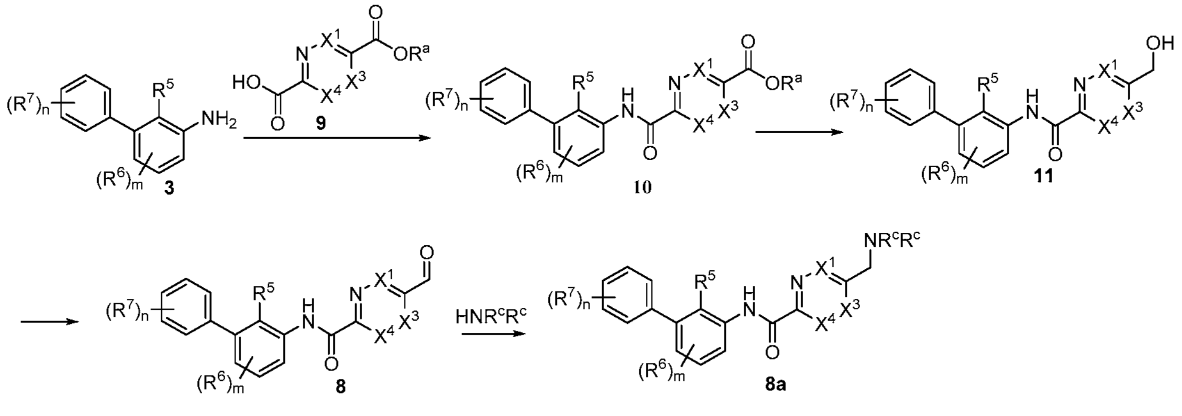
Scheme 1

Compounds of the invention (**8a**) can be synthesized using a process shown in Scheme 2. The aromatic amine **3** is reacted with an acid of formula **5** under suitable conditions forming an amide bond to provide the product **6**, using coupling reagents such as, but not limited to, HATU and DIPEA. The compound of formula **7** can be synthesized by coupling the halo group (W_2) of **6** with a vinyl reagent (*e.g.*, vinyl boronic acid pinacol ester) under standard coupling reaction conditions (such as Suzuki coupling reaction, *e.g.*, in the presence of a palladium catalyst (*e.g.*, 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) and a base (*e.g.*, a bicarbonate or a carbonate base)). The vinyl group in compound **7** is oxidatively cleaved to afford an aldehyde of formula **8** in the presence of suitable reagents such as, but not limited to, OsO_4 and $NaIO_4$. Then compounds of formula **8a** are obtained by a reductive amination between the compound of formula **8** and a suitable amine in a proper solvent such as THF or DCM using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid.



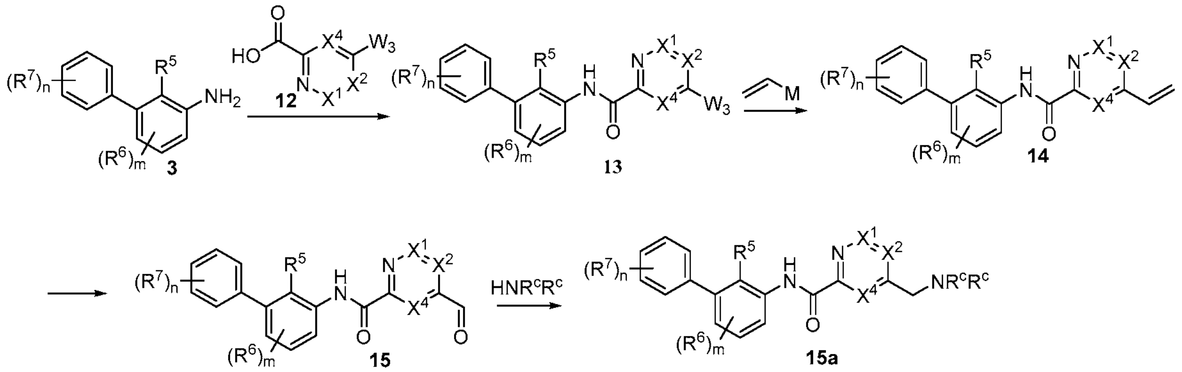
Scheme 2

Compounds of formula **8a** can be alternatively synthesized using a process shown in Scheme 3. The aromatic amine **3** is reacted with an acid of formula **9** under suitable conditions to form an amide bond providing the product of formula **10**, using coupling reagents such as, but not limited to, HATU and DIPEA. Subsequent reduction of the ester group in compound **10** can give an alcohol of formula **11** using a suitable reducing agent such as, but not limited to, lithium aluminum hydride. The alcohol unit in compound **11** was oxidized to aldehyde in compound **8** with a suitable oxidant such as, but not limited to, Dess-Martin periodinane. Then the compound of formula **8a** was obtained by a reductive amination between formula **8** and a suitable amine in a proper solvent such as THF or DCM using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid.



Scheme 3

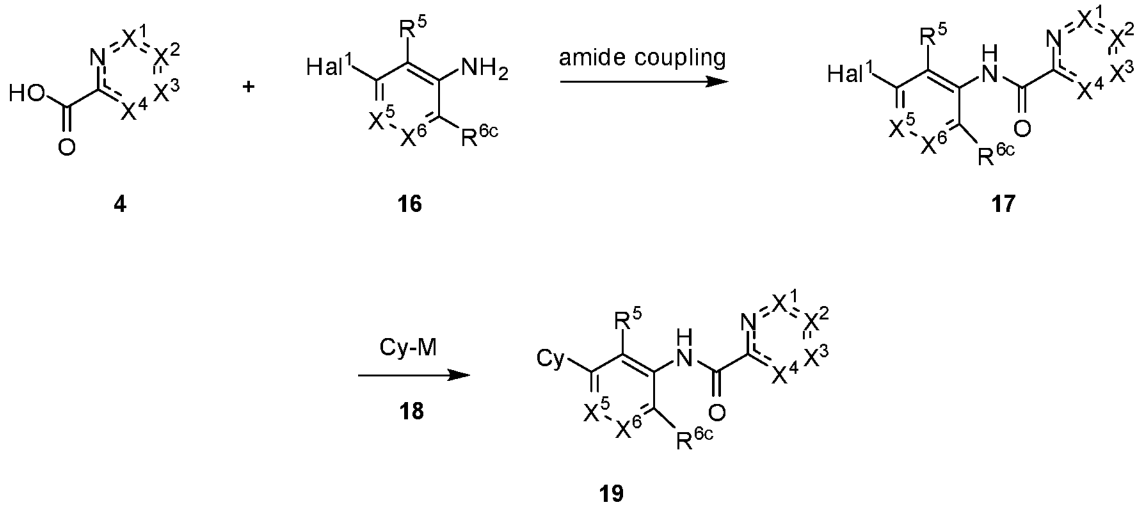
Compounds of the invention (**15a**) can be synthesized using a process shown in Scheme 4. The aromatic amine **3** is reacted with an acid of formula **12** under suitable conditions forming an amide bond to provide the product of formula **13**, using coupling reagents such as, but not limited to, HATU and DIPEA. The compound of formula **14** can be synthesized by coupling the halo group (W_3) of **13** with a vinyl reagent (*e.g.*, vinyl boronic acid pinacol ester) under standard coupling reaction conditions (such as Suzuki coupling reaction, *e.g.*, in the presence of a palladium catalyst (*e.g.*, 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) and a base (*e.g.*, a bicarbonate or a carbonate base)). The vinyl group in compound **14** is oxidatively cleaved to afford an aldehyde of formula **15** in the presence of suitable reagents such as, but not limited to, OsO_4 and $NaIO_4$. Then the compound of formula **15a** is obtained by a reductive amination between the compound of formula **15** and a suitable amine in a proper solvent such as THF or DCM using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid.



Scheme 4

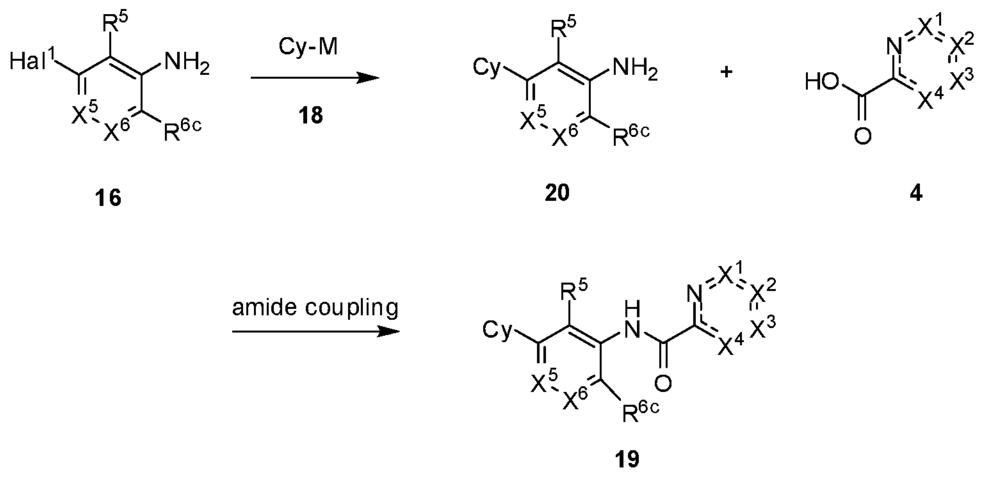
Compounds of Formula **19** can be prepared using procedures as outlined in Scheme **5**. Acids of formula **4** can react with aromatic amines of formula **16** under amide coupling conditions [e.g., in the presence of 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) and a suitable base such as N,N-Diisopropylethylamine (DIPEA)] to give amide derivatives of formula **17**. The halide (e.g., Hal^1 = Cl, Br, I) in compounds **17** can be coupled to compounds of formula **18**, 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 **19**. Alternatively, compound **18** can be a cyclic amine (where M is H and attached to an amine nitrogen in ring A) and the coupling of aryl halide **17** with the cyclic amine **18** 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 5



Alternatively, compounds of formula **19** can also be prepared using reaction sequence as outlined in Scheme **6**. Coupling of aromatic halides of formula **16** with compounds of formula **18** can be achieved under similar conditions as described in Scheme **5** (e.g., conditions used for coupling of compounds **17** and compounds **18**) to give compounds of formula **20**. Acids of formula **4** can react with aromatic amines of formula **20** under amide coupling conditions to give compounds of formula **19**.

Scheme 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). 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 or chronic infection, including enhancement of response to vaccination. In some embodiments, the present disclosure provides a method for inhibiting the PD-1/PD-L1 protein/protein interaction. The method includes administering to an individual or a patient a compound of Formula (I'), 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 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'), Formula (I) or a salt or stereoisomer thereof such that growth of cancerous tumors is inhibited. A compound of Formula (I'), 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'), 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'), 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'), 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'), 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'), Formula (I) or any of the formulas as described herein, a compound or composition as recited in any of the claims and described herein, or a salt thereof.

Examples of cancers that are treatable using the compounds or combinations of the present disclosure include, but are not limited to, ewing sarcoma, cholangiocarcinoma ,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 or combinations 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, colon cancer and lung cancer (e.g. non-small cell lung cancer). 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 or combinations 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.

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'), 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'), 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'), 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'), 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, CSFIR, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, Ron, Sea, TRKA, TRKB, TRKC, FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. 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 and NLG919), an LSD1 inhibitor (e.g., INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor, a PI3K-gamma inhibitor, such as PI3K-gamma selective inhibitor (e.g., INCB50797), a Pim inhibitor, a CSF1R inhibitor, a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer), 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) 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.

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 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 or MK-4166.

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. 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, 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, 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.

In some embodiments, the anti-cancer 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).

Compounds of the present disclosure can be used in combination with one or more immune checkpoint inhibitors for the treatment of diseases, such as cancer or infections. 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 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.

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 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 or MK-4166.

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. In some embodiments, the OX40L fusion protein is MEDI6383.

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'), 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'), 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'), 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'), 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’), 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 an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). It is to be understood that a "radio-labeled" compound is a compound that has incorporated at least 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.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.

Specifically, a 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 (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

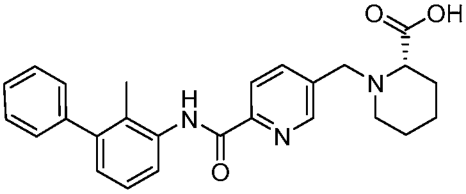
The present disclosure also includes pharmaceutical kits useful, *e.g.*, in the treatment or prevention of diseases or disorders associated with the activity of PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80), such as cancer or infections, which include one or more containers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

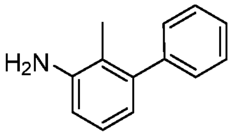
EXAMPLES

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-[(6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid

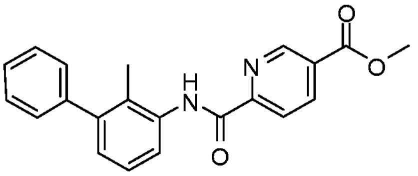


Step 1: 2-methylbiphenyl-3-amine



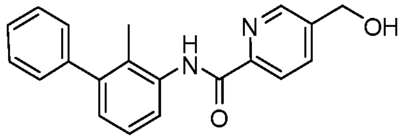
Tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.3 mmol) was added to a mixture of 3-bromo-2-methylaniline (1000 mg, 5 mmol), phenylboronic acid (600 mg, 5 mmol), 1,4-dioxane (20 mL, 200 mmol) and water (3 mL, 200 mmol), and the mixture was allowed to stir at 100 °C overnight. After concentration, the residue was dissolved in dichloromethane (DCM) and washed with brine. The organic layer was dried and concentrated to afford the desired product as a brown solid, which was used in the next step without further purification. LC-MS calculated for $C_{13}H_{14}N$ $(M+H)^+$: m/z = 184.1; found 184.1.

Step 2: methyl 6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}nicotinate



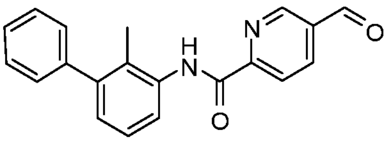
N,N-Diisopropylethylamine (200 μL, 1 mmol) was added to a mixture of 2-methylbiphenyl-3-amine (70 mg, 0.4 mmol), 5-(methoxycarbonyl)pyridine-2-carboxylic acid (Oakwood Chemical, cat#017196, 75 mg, 0.42 mmol), and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (220 mg, 0.57 mmol) in N,N-dimethylformamide (2 mL, 20 mmol). The reaction mixture was allowed to stir at room temperature (rt) overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-35%) to afford the desired product. LC-MS calculated for $C_{21}H_{19}N_2O_3$ $(M+H)^+$: m/z = 347.1; found 347.1.

Step 3: 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



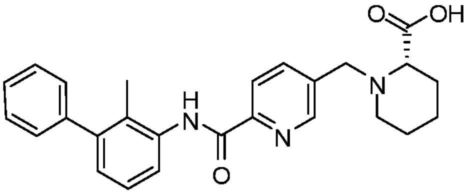
1.0 M Lithium tetrahydroaluminate in THF (0.6 mL, 0.6 mmol) was added to a THF (4.0 mL) solution of methyl 6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}nicotinate (100 mg, 0.3 mmol) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 1 h to reach full conversion. The mixture was quenched with aqueous potassium sodium tartrate. The mixture was allowed to stir at rt for 2h. The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was dried, concentrated, and the residue was used in the next step without further purification. LC-MS calculated for $C_{20}H_{19}N_2O_2$ $(M+H)^+$: m/z = 319.1; found 319.0.

Step 4: 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



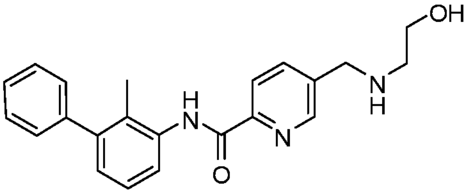
Dess-Martin periodinane (76 mg, 0.18 mmol) was added to a mixture of 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (48 mg, 0.15 mmol), sodium bicarbonate (40 mg, 0.4 mmol), and methylene chloride (1 mL, 20 mmol), and the mixture was allowed to stir at rt for 2 h to reach full conversion. After concentration, the residue was dissolved in DCM and filtered. The organic layer was concentrated to afford desired product which was used in the next step without further purification. LC-MS calculated for $C_{20}H_{17}N_2O_2$ $(M+H)^+$: m/z = 317.1; found 317.0.

Step 5: (2S)-1-[(6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid



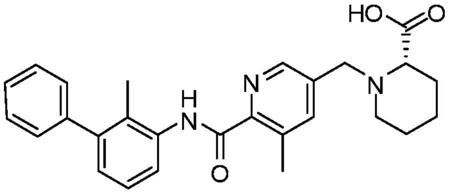
(2S)-Piperidine-2-carboxylic acid (20 mg, 0.1 mmol), sodium triacetoxyborohydride (60 mg, 0.3 mmol) and one drop of acetic acid were added to a methylene chloride (1 mL) solution of 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide, and the mixture was allowed to stir at rt overnight. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{26}H_{28}N_3O_3$ $(M+H)^+$: m/z = 430.2; found 430.2.

Example 2: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

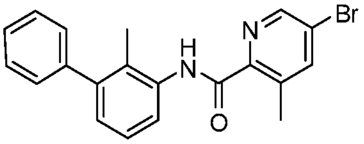


Ethanolamine (20 µL, 0.3 mmol) and sodium triacetoxyborohydride (60 mg, 0.3 mmol) were added to a methylene chloride (1 mL) solution of 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (Example 1, Step 4), and the mixture was allowed to stir at rt overnight. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{22}H_{24}N_3O_2$ $(M+H)^+$: m/z = 362.2; found 362.2.

Example 3: (2S)-1-[(5-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid

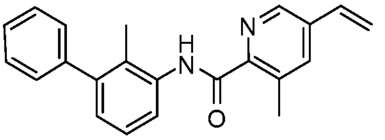


Step 1: 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



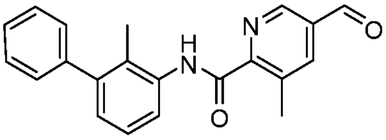
This compound was prepared using a similar procedure as described for Example 1, Step 2 with 5-bromo-2-carboxy-3-methylpyridine replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{20}H_{18}BrN_2O$ $(M+H)^+$: m/z = 381.0; found: 381.1.

Step 2: 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



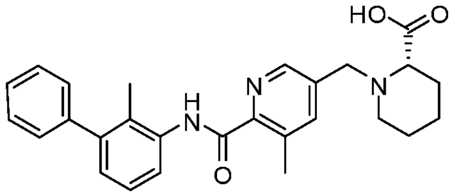
A mixture of 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (150 mg, 0.39 mmol), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with DCM (20 mg, 0.02 mmol), sodium bicarbonate, and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (70 µL, 0.4 mmol) in dioxane (2.83 mL, 29.6 mmol) and water (1 mL, 60 mmol) was degassed and sealed. It was stirred at 95 °C overnight. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was separated and concentrated to afford desired product, which was used in the next step without further purification. LC-MS calculated for $C_{22}H_{21}N_2O$ $(M+H)^+$: m/z = 329.2; found: 329.2.

Step 3: 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



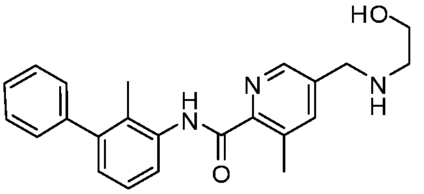
3-Methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide (100 mg, 0.4 mmol) was dissolved in 1,4-dioxane (6 mL, 80 mmol) and water (1 mL, 70 mmol). To this mixture was added a mixture of osmium tetraoxide (4% *w/w* in water, 0.38 mL, 0.06 mmol). After stirring for 5 min, sodium periodate (342 mg, 1.60 mmol) was added and the mixture was allowed to stir for 1 h to reach full conversion. The reaction mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford desired product, which was used in the next step without further purification. LC-MS calculated for $C_{21}H_{19}N_2O_2$ $(M+H)^+$: m/z = 331.1; found: 331.1.

Step 4: (2S)-1-[(5-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid



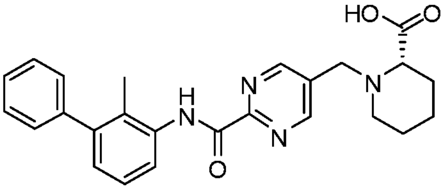
This compound was prepared using a similar procedure as described for Example 1, Step 5, with 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{27}H_{30}N_3O_3$ $(M+H)^+$: m/z = 444.2; found 444.2.

Example 4: 5-{[(2-hydroxyethyl)amino]methyl}-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

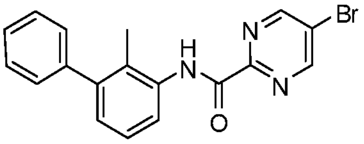


Ethanolamine (20 µL, 0.3 mmol) and sodium triacetoxyborohydride (60 mg, 0.3 mmol) were added to a methylene chloride (1 mL) solution of 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (Example 3, Step 3), and the mixture was allowed to stir at rt overnight. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{23}H_{26}N_3O_2$ $(M+H)^+$: m/z = 376.2; found 376.1.

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

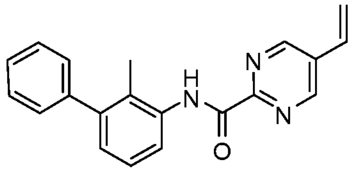


Step 1: 5-bromo-N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide



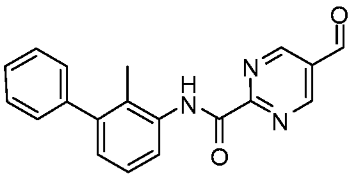
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 5-bromopyrimidine-2-carboxylic acid (Ark Pharma, cat#AK-21808) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{18}H_{15}BrN_3O$ $(M+H)^+$: m/z = 368.0; found 368.0.

Step 2: N-(2-methylbiphenyl-3-yl)-5-vinylpyrimidine-2-carboxamide



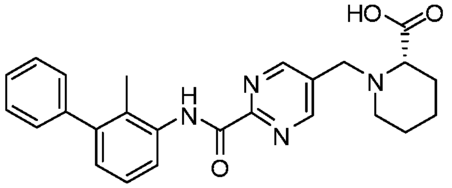
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{20}H_{18}N_3O$ $(M+H)^+$: m/z = 316.1; found 316.1.

Step 3: 5-formyl-N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide



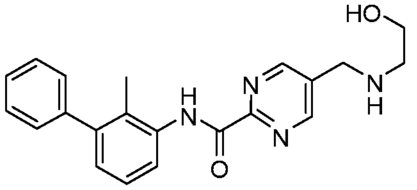
This compound was prepared using a similar procedure as described for Example 3, Step 3, with N-(2-methylbiphenyl-3-yl)-5-vinylpyrimidine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{19}H_{16}N_3O_2$ $(M+H)^+$: m/z = 318.2; found 318.1.

Step 4: (2S)-1-[(2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyrimidin-5-yl)methyl]piperidine-2-carboxylic acid



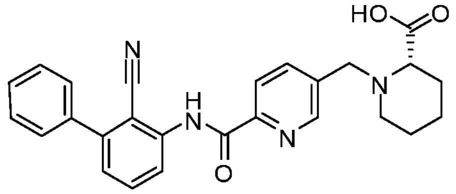
This compound was prepared using a similar procedure as described for Example 1, Step 5, with 5-formyl-N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide replacing 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{25}H_{27}N_4O_3$ $(M+H)^+$: m/z = 431.2; found 431.1.

Example 6: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide

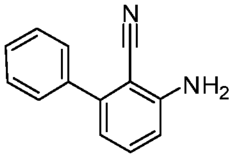


This compound was prepared using a similar procedure as described for Example 4 with 5-formyl-N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide (Example 5, Step 3) replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{21}H_{23}N_4O_2$ $(M+H)^+$: m/z = 363.2; found 363.2.

Example 7: (2S)-1-[(6-{[(2-cyanobiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid

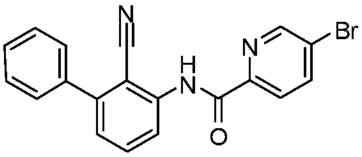


Step 1: 3-aminobiphenyl-2-carbonitrile



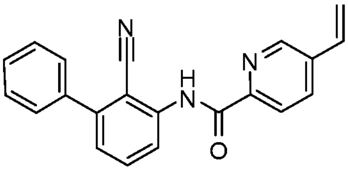
This compound was prepared using a similar procedure as described for Example 1, Step 1, with 2-amino-6-bromobenzonitrile (Astatech, cat#CL8148) replacing 3-bromo-2-methylaniline. LC-MS calculated for $C_{13}H_{11}N_2$ $(M+H)^+$: m/z = 195.1; found 195.1.

Step 2: 5-bromo-N-(2-cyanobiphenyl-3-yl)pyridine-2-carboxamide



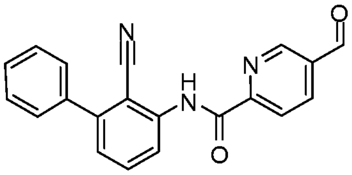
N,N-Diisopropylethylamine (200 µL, 1 mmol) was added to a mixture of 3-aminobiphenyl-2-carbonitrile (80 mg, 0.4 mmol), 5-bromopyridine-2-carboxylic acid (Frontier Scientific cat#B1704, 96 mg, 0.47 mmol), and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (250 mg, 0.65 mmol) in N,N-dimethylformamide (2 mL, 20 mmol). The reaction mixture was allowed to stir at rt overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-35%) to afford the desired product. LC-MS calculated for $C_{19}H_{13}BrN_3O$ $(M+H)^+$: m/z = 378.0; found 378.0.

Step 3: N-(2-cyanobiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



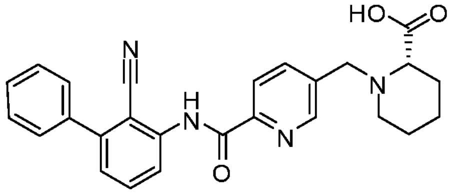
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-N-(2-cyanobiphenyl-3-yl)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{21}H_{16}N_3O$ $(M+H)^+$: m/z = 326.1; found 326.1.

Step 4: N-(2-cyanobiphenyl-3-yl)-5-formylpyridine-2-carboxamide



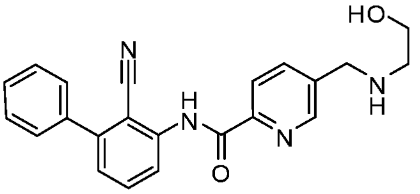
This compound was prepared using a similar procedure as described for Example 3, Step 3, with N-(2-cyanobiphenyl-3-yl)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{20}H_{14}N_3O_2$ $(M+H)^+$: m/z = 328.1; found 328.1.

Step 5: (2S)-1-[(6-{[(2-cyanobiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid



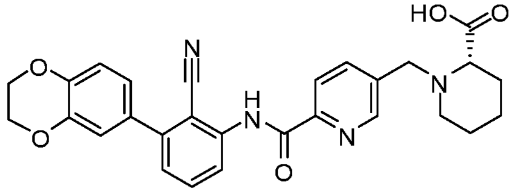
This compound was prepared using a similar procedure as described for Example 1, Step 5, with N-(2-cyanobiphenyl-3-yl)-5-formylpyridine-2-carboxamide replacing 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{26}H_{25}N_4O_3$ $(M+H)^+$: m/z = 441.2; found 441.1.

Example 8: N-(2-cyanobiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide

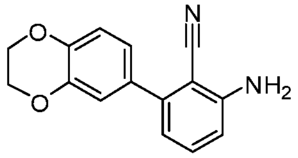


This compound was prepared using a similar procedure as described for Example 4 with N-(2-cyanobiphenyl-3-yl)-5-formylpyridine-2-carboxamide (Example 7, Step 4) replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{22}H_{21}N_4O_2$ $(M+H)^+$: m/z = 373.2; found 373.2.

Example 9: (2S)-1-{[6-({[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]amino}carbonyl)pyridin-3-yl]methyl}piperidine-2-carboxylic acid

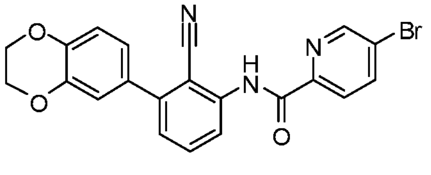


Step 1: 2-amino-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile



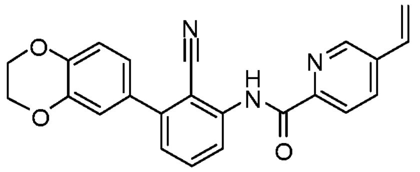
This compound was prepared using a similar procedure as described for Example 1, Step 1, with 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (Sigma-Aldrich, cat#635995) replacing phenylboronic acid, and with 2-amino-6-bromobenzonitrile (Astatech, cat#CL8148) replacing 3-bromo-2-methylaniline. LC-MS calculated for $C_{15}H_{13}N_2O_2$ $(M+H)^+$: m/z = 253.1; found 253.1.

Step 2: 5-bromo-N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]pyridine-2-carboxamide



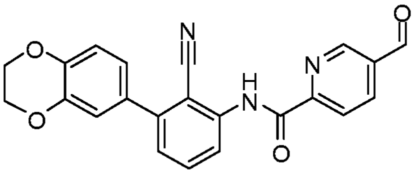
N,N-Diisopropylethylamine (200 μL, 1 mmol) was added to a mixture of 2-amino-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile (100 mg, 0.4 mmol), 5-bromopyridine-2-carboxylic acid (Frontier Scientific cat#B1704, 96 mg, 0.47 mmol), and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (250 mg, 0.65 mmol) in N,N-dimethylformamide (2 mL, 20 mmol). The reaction mixture was allowed to stir at rt overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-35%) to afford the desired product. LC-MS calculated for $C_{21}H_{15}BrN_3O_3$ $(M+H)^+$: m/z = 436.0; found 436.0.

Step 3: N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-vinylpyridine-2-carboxamide



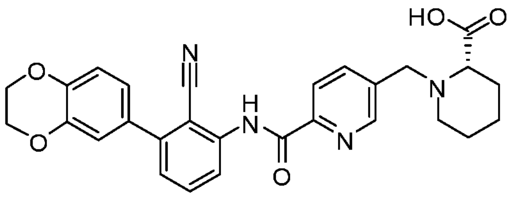
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{23}H_{18}N_3O_3$ $(M+H)^+$: m/z = 384.1; found 384.1.

Step 4: N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-formylpyridine-2-carboxamide



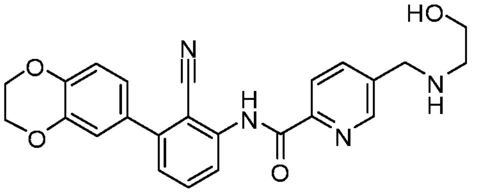
This compound was prepared using a similar procedure as described for Example 3, Step 3, with N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{22}H_{16}N_3O_4$ $(M+H)^+$: m/z = 386.1; found 386.1.

Step 5: (2S)-1-{[6-({[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]amino}carbonyl)pyridin-3-yl]methyl}piperidine-2-carboxylic acid



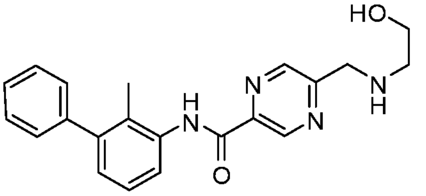
This compound was prepared using a similar procedure as described for Example 1, Step 5, with N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-formylpyridine-2-carboxamide replacing 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{28}H_{27}N_4O_5$ $(M+H)^+$: m/z = 499.2; found 499.2.

Example 10: N-(2-cyano-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-5-((2-hydroxyethylamino)methyl)picolinamide

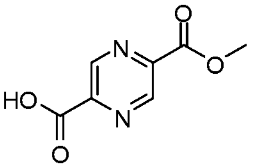


This compound was prepared using a similar procedure as described for Example 4 with N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-formylpyridine-2-carboxamide (Example 9, Step 4) replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{22}H_{21}N_4O_2$ $(M+H)^+$: m/z = 431.2; found 431.2.

Example 11: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide

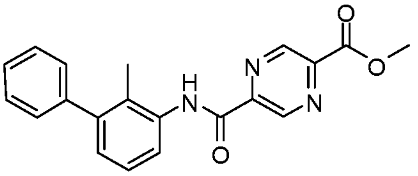


Step 1: pyrazine-2,5-dicarboxylic acid



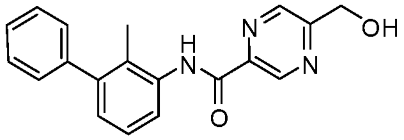
Sulfuric acid (19 μL, 0.36 mmol) was added to a methanol (1.2 mL, 29 mmol) solution of pyrazine-2,5-dicarboxylic acid (Ark Pharma cat# AK-76746, 100 mg, 0.6 mmol). Then the mixture was allowed to stir at 90 °C overnight. After cooling to rt, the mixture was diluted with methanol and basified with NaOH aq. Then the mixture was allowed to stir at rt for 5 h to reach ~50% conversion to afford the mono-ester. Then the mixture was acidified with HCl aq, and extracted with DCM/iPrOH x 3. The organic layer was dried and concentrated to afford desired product, which was used in the next step without further purification. LC-MS calculated for $C_7H_7N_2O_4$ $(M+H)^+$: m/z = 183.0; found 183.0.

Step 2: methyl 5-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyrazine-2-carboxylate



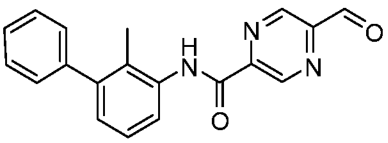
This compound was prepared using a similar procedure as described for Example 1, Step 2, with pyrazine-2,5-dicarboxylic acid replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{20}H_{18}N_3O_3$ $(M+H)^+$: m/z = 348.1; found 348.1.

Step 3: 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide



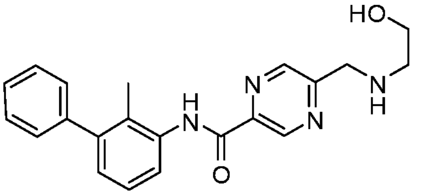
This compound was prepared using a similar procedure as described for Example 1, Step 3, with methyl 5-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyrazine-2-carboxylate replacing methyl 6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}nicotinate. Part of the reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{19}H_{18}N_3O_2$ $(M+H)^+$: m/z = 320.1; found 320.1.

Step 4: 5-formyl-N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide



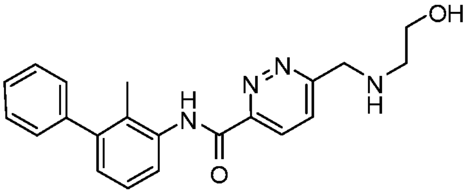
This compound was prepared using a similar procedure as described for Example 1, Step 4, with 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide replacing 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamid. LC-MS calculated for $C_{19}H_{16}N_3O_2$ $(M+H)^+$: m/z = 318.1; found 318.1.

Step 5: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide

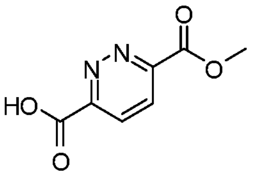


This compound was prepared using a similar procedure as described for Example 4 with 5-formyl-N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{21}H_{23}N_4O_2$ $(M+H)^+$: m/z = 363.2; found 363.2.

Example 12: 6-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide

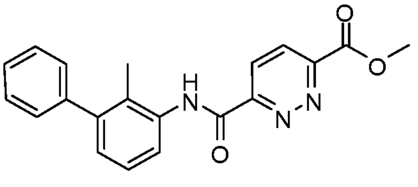


Step 1: 6-(methoxycarbonyl)pyridazine-3-carboxylic acid



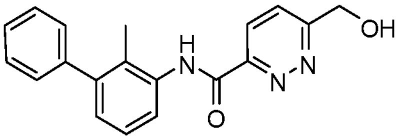
This compound was prepared using a similar procedure as described for Example 11, Step 1, with pyridazine-3,6-dicarboxylic acid (Astatech, *cat# 37156*) replacing pyrazine-2,5-dicarboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_7H_7N_2O_4$ $(M+H)^+$: m/z = 183.0; found 183.0.

Step 2: methyl 6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridazine-3-carboxylate



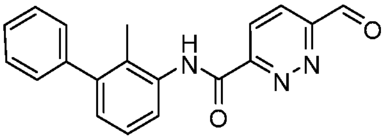
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 6-(methoxycarbonyl)pyridazine-3-carboxylic acid replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{21}H_{17}N_3O_3$ $(M+H)^+$: m/z = 348.1; found 348.1.

Step 3: 6-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide



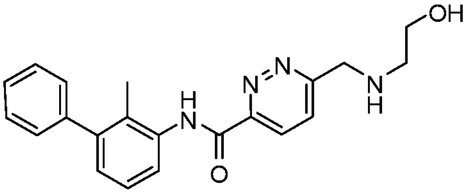
This compound was prepared using a similar procedure as described for Example 1, Step 3, with methyl 6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridazine-3-carboxylate replacing methyl 6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}nicotinate. LC-MS calculated for $C_{19}H_{18}N_3O_2$ $(M+H)^+$: m/z = 320.1; found 320.1.

Step 4: 6-formyl-N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide



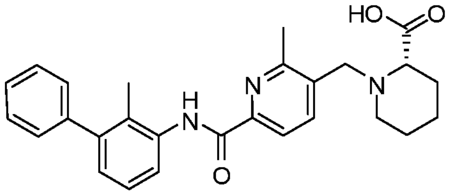
This compound was prepared using a similar procedure as described for Example 1, Step 4, with 6-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide replacing 5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{19}H_{16}N_3O_2$ $(M+H)^+$: m/z = 318.1; found 318.1.

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

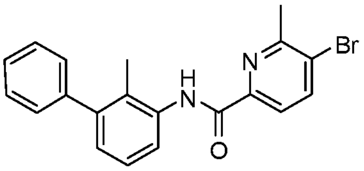


This compound was prepared using a similar procedure as described for Example 4 with 6-formyl-N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH4OH) to give the desired product. LC-MS calculated for $C_{21}H_{23}N_4O_2$ $(M+H)^+$: m/z = 363.2; found 363.2.

Example 13: (2S)-1-[(2-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid

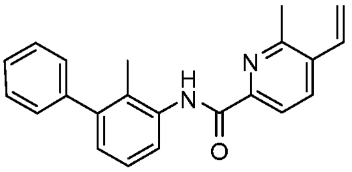


Step 1: 5-bromo-6-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



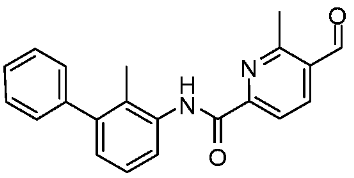
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 5-bromo-6-methylpyridine-2-carboxylic acid (Ark Pharma cat#Ak-61563) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{20}H_{18}BrN_2O$ $(M+H)^+$: m/z = 381.0; found 381.0.

Step 2: 6-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



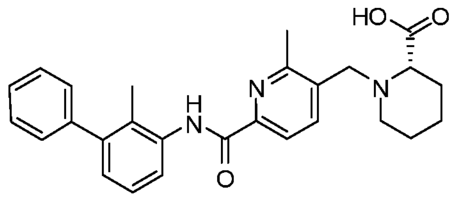
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-6-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{22}H_{21}N_2O$ $(M+H)^+$: m/z = 329.2; found 329.2.

Step 3: 5-formyl-6-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



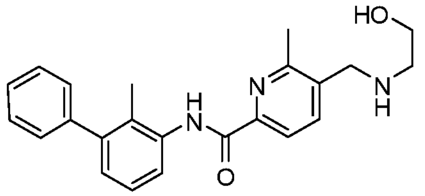
This compound was prepared using a similar procedure as described for Example 3, Step 3, with 6-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{21}H_{19}N_2O_2$ $(M+H)^+$: m/z = 331.1; found 331.1.

Step 4: (2S)-1-[(2-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid



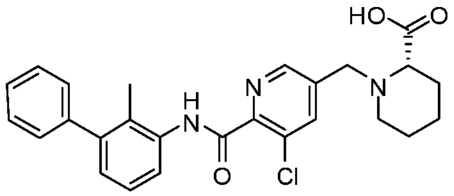
This compound was prepared using a similar procedure as described for Example 1, Step 5, with 5-formyl-6-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{27}H_{30}N_3O_3$ $(M+H)^+$: m/z = 444.2; found 444.2.

Example 14: 5-{[(2-hydroxyethyl)amino]methyl}-6-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

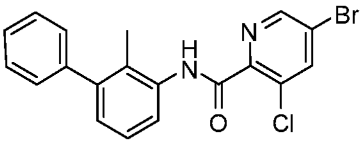


This compound was prepared using a similar procedure as described for Example 4 with 5-formyl-6-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (Example 13, Step 3) replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{23}H_{26}N_3O_2$ $(M+H)^+$: m/z = 376.2; found 376.2.

Example 15: (2S)-1-[(5-chloro-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid

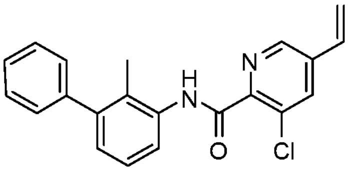


Step 1: 5-bromo-3-chloro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



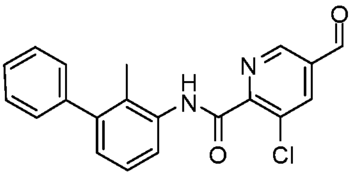
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 5-bromo-3-chloropyridine-2-carboxylic acid (Ark Pharma cat#AK-53906) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{19}H_{15}BrClN_2O$ (M+H)$^+$: m/z = 401.0; found 401.1.

Step 2: 3-chloro-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



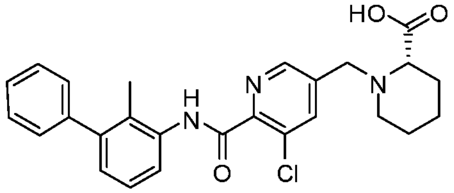
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-3-chloro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{21}H_{18}ClN_2O$ (M+H)$^+$: m/z = 349.1; found 349.0.

Step 3: 3-chloro-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



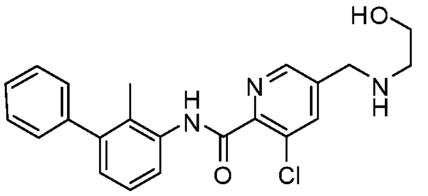
This compound was prepared using a similar procedure as described for Example 3, Step 3, with 3-chloro-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{20}H_{16}ClN_2O_2$ (M+H)$^+$: m/z = 351.1; found 351.0.

Step 4: (2S)-1-[(5-chloro-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid



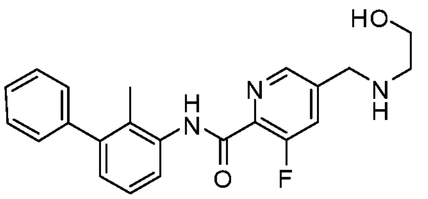
This compound was prepared using a similar procedure as described for Example 1, Step 5 with 3-chloro-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{26}H_{27}ClN_3O_3$ $(M+H)^+$: m/z = 464.2; found 464.0.

Example 16: 3-chloro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

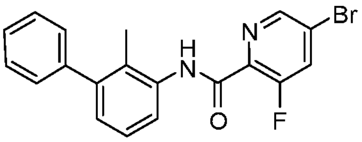


This compound was prepared using a similar procedure as described for Example 4 with 3-chloro-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (Example 15, Step 3) replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{22}H_{23}ClN_3O_2$ $(M+H)^+$: m/z = 396.1; found 396.1.

Example 17: 3-fluoro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

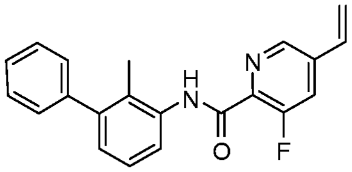


Step 1: 5-bromo-3-fluoro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



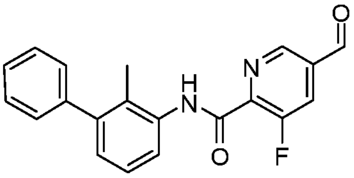
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 5-bromo-3-fluoropyridine-2-carboxylic acid (Aldrich, cat#753483) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid and prolong the reaction time to 3 days. LC-MS calculated for $C_{19}H_{15}BrFN_2O$ $(M+H)^+$: m/z = 385.0; found 385.0.

Step 2: 3-fluoro-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



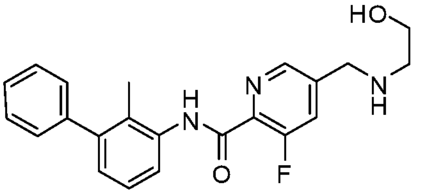
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-3-fluoro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{21}H_{18}FN_2O$ $(M+H)^+$: m/z = 333.1; found 333.1.

Step 3: 3-fluoro-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



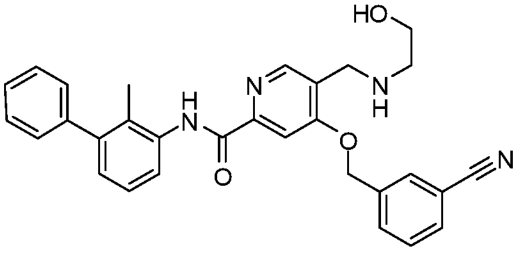
This compound was prepared using a similar procedure as described for Example 3, Step 3, with 3-fluoro-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{20}H_{16}FN_2O_2$ $(M+H)^+$: m/z = 335.1; found 335.1.

Step 4: 3-fluoro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

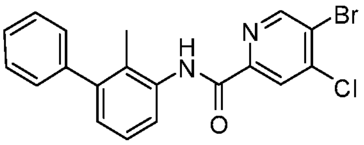


This compound was prepared using a similar procedure as described for Example 4 with 3-fluoro-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{22}H_{23}FN_3O_2$ $(M+H)^+$: m/z = 380.2; found 380.2.

Example 18: 4-[(3-cyanobenzyl)oxy]-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

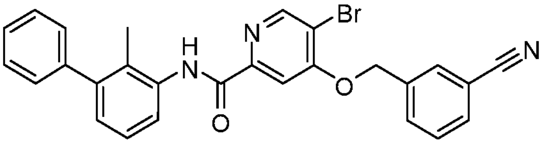


Step 1: 5-bromo-4-chloro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



This compound was prepared using a similar procedure as described for Example 1, Step 2 with 5-bromo-4-chloropyridine-2-carboxylic acid (Ark Pharma, cat#AK-55136) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{19}H_{15}BrClN_2O$ $(M+H)^+$: m/z = 401.0; found 401.0.

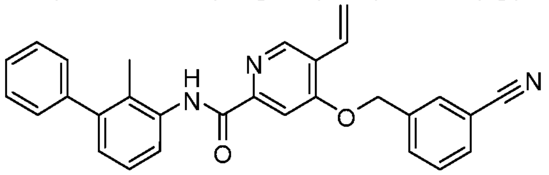
Step 2: 5-bromo-4-[(3-cyanobenzyl)oxy]-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



Sodium hydride (60% w/w in oil, 9 mg, 0.4 mmol) was added to a mixture of 5-bromo-4-chloro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (50 mg, 0.1 mmol), 3-(hydroxymethyl)benzonitrile (TCI cat#C1510, 40 mg, 0.30 mmol) and N,N-dimethylformamide (1 mL, 10 mmol) at rt. Then the mixture was allowed to stir at room temperature for 4 h to reach full conversion. The mixture was quenched with water and extracted with EtOAc x 3, and the combined organic layers were dried and concentrated to afford desired product. LC-MS calculated for $C_{27}H_{21}BrN_3O_2$ $(M+H)^+$: m/z = 498.1; found

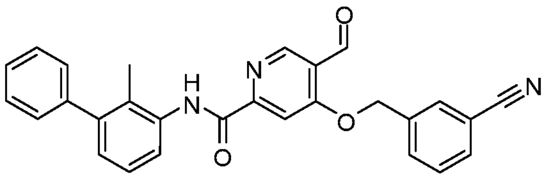
498.1.

Step 3: 4-[(3-cyanobenzyl)oxy]-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



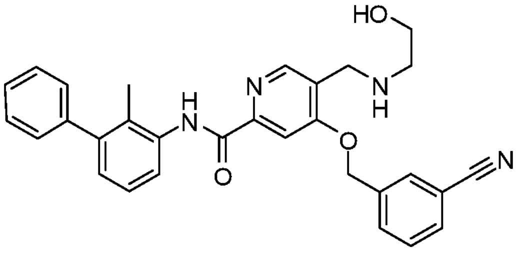
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-4-[(3-cyanobenzyl)oxy]-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{29}H_{24}N_3O_2$ $(M+H)^+$: m/z = 446.2; found 446.1.

Step 4: 4-[(3-cyanobenzyl)oxy]-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



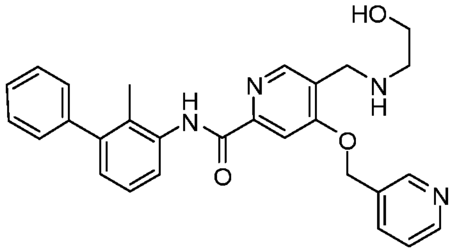
This compound was prepared using a similar procedure as described for Example 3, Step 3, with 4-[(3-cyanobenzyl)oxy]-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{28}H_{22}N_3O_3$ $(M+H)^+$: m/z = 448.2; found 448.1.

Step 5: 4-[(3-cyanobenzyl)oxy]-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

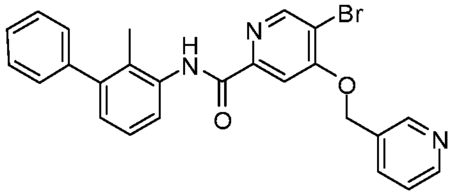


This compound was prepared using a similar procedure as described for Example 4 with 4-[(3-cyanobenzyl)oxy]-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{30}H_{29}N_4O_3$ $(M+H)^+$: m/z = 493.2; found 493.2.

Example 19: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)pyridine-2-carboxamide

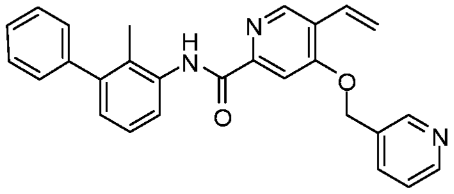


Step 1: 5-bromo-N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)pyridine-2-carboxamide



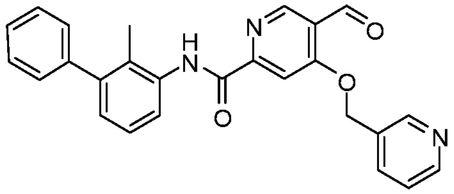
This compound was prepared using a similar procedure as described for Example 18, Step 2, with nicotinyl alcohol replacing 3-(hydroxymethyl)benzonitrile. LC-MS calculated for $C_{25}H_{21}BrN_3O_2$ $(M+H)^+$: m/z = 474.0; found 474.1.

Step 2: N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)-5-vinylpyridine-2-carboxamide



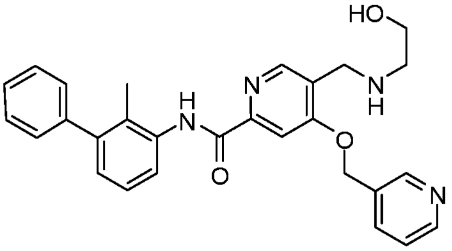
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{27}H_{24}N_3O_2$ $(M+H)^+$: m/z = 422.2; found 422.1.

Step 3: 5-formyl-N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)pyridine-2-carboxamide



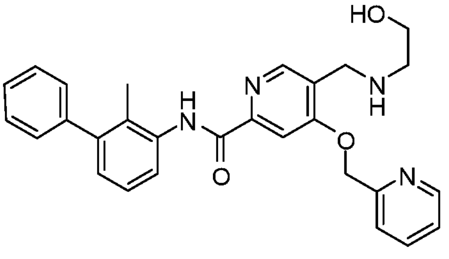
This compound was prepared using a similar procedure as described for Example 3, Step 3, with N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{26}H_{22}N_3O_3$ $(M+H)^+$: m/z = 424.2; found 424.2.

Step 4: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)pyridine-2-carboxamide

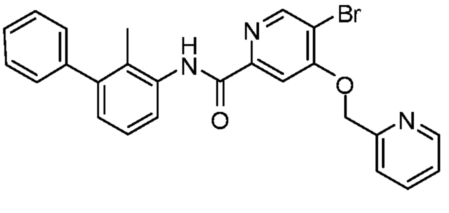


This compound was prepared using a similar procedure as described for Example 4 with 5-formyl-N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)pyridine-2-carboxamide replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product, which was further purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{28}H_{29}N_4O_3$ $(M+H)^+$: m/z = 469.2; found 469.2.

Example 20: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)pyridine-2-carboxamide

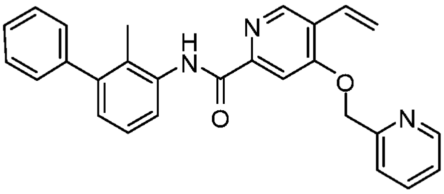


Step 1: 5-bromo-N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)pyridine-2-carboxamide



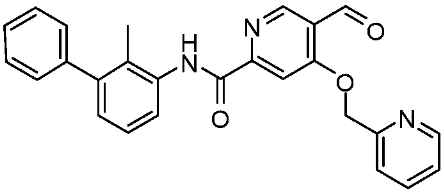
This compound was prepared using a similar procedure as described for Example 18, Step 2, with pyridin-2-ylmethanol replacing 3-(hydroxymethyl)benzonitrile. LC-MS calculated for $C_{25}H_{21}BrN_3O_2$ $(M+H)^+$: m/z = 474.0; found 474.1.

Step 2: N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)-5-vinylpyridine-2-carboxamide



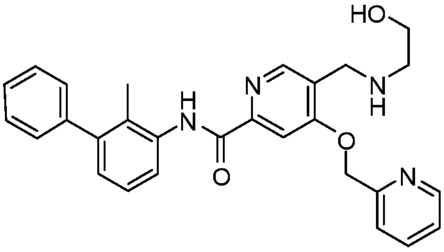
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{27}H_{24}N_3O_2$ $(M+H)^+$: m/z = 422.2; found 422.1.

Step 3: 5-formyl-N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)pyridine-2-carboxamide



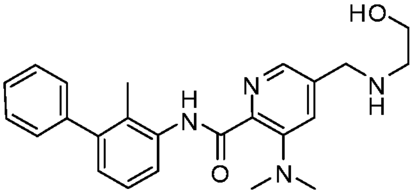
This compound was prepared using a similar procedure as described for Example 3, Step 3, with N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{26}H_{22}N_3O_3$ $(M+H)^+$: m/z = 424.2; found 424.2.

Step 4: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)pyridine-2-carboxamide

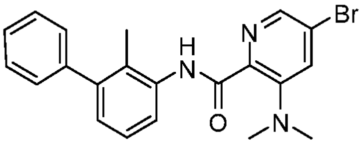


This compound was prepared using a similar procedure as described for Example 4 with 5-formyl-N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)pyridine-2-carboxamide replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{28}H_{29}N_4O_3$ $(M+H)^+$: m/z = 469.2; found 469.2.

Example 21: 3-(dimethylamino)-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

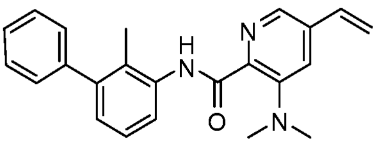


Step 1: 5-bromo-3-(dimethylamino)-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



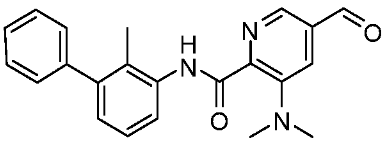
1.0 M Dimethylamine in THF (0.3 mL, 0.3 mmol) was added to 5-bromo-3-fluoro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (Example 17, Step 1, 40 mg, 0.1 mmol) at rt, then the reaction was allowed to stir at rt overnight. The reaction was concentrated to afford desired product, which was used in the next step without further purification. LC-MS calculated for $C_{21}H_{21}BrN_3O$ $(M+H)^+$: m/z = 410.1; found 410.1.

Step 2: 3-(dimethylamino)-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



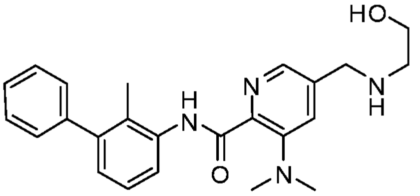
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 5-bromo-3-(dimethylamino)-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{23}H_{24}N_3O$ $(M+H)^+$: m/z = 358.2; found 358.1.

Step 3: 3-(dimethylamino)-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



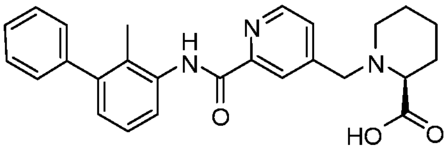
This compound was prepared using a similar procedure as described for Example 3, Step 3, with 3-(dimethylamino)-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{22}H_{22}N_3O_2$ $(M+H)^+$: m/z = 360.2; found 360.1.

Step 4: 3-(dimethylamino)-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

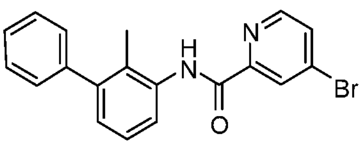


This compound was prepared using a similar procedure as described for Example 4 with 3-(dimethylamino)-5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{24}H_{29}N_4O_2$ $(M+H)^+$: m/z = 405.2; found 405.2.

Example 22: (2S)-1-[(2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-4-yl)methyl]piperidine-2-carboxylic acid

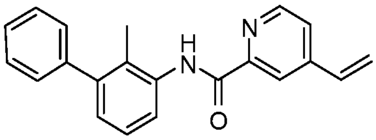


Step 1: 4-bromo-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



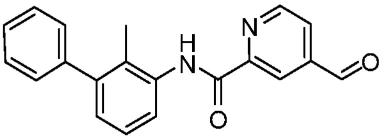
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 4-bromopyridine-2-carboxylic acid (Ark Pharm, cat#AK-23753) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{19}H_{16}BrN_2O$ $(M+H)^+$: m/z = 367.0; found 367.0.

Step 2: N-(2-methylbiphenyl-3-yl)-4-vinylpyridine-2-carboxamide



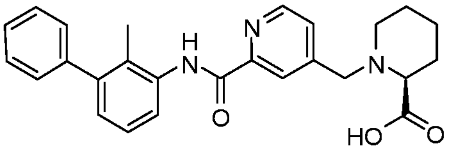
This compound was prepared using a similar procedure as described for Example 3, Step 2, with 4-bromo-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. LC-MS calculated for $C_{21}H_{19}N_2O$ $(M+H)^+$: m/z = 315.1; found 315.2.

Step 3: 4-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



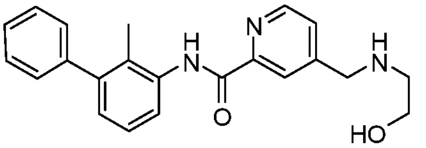
This compound was prepared using a similar procedure as described for Example 3, Step 3, with N-(2-methylbiphenyl-3-yl)-4-vinylpyridine-2-carboxamide replacing 3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide. LC-MS calculated for $C_{20}H_{17}N_2O_2$ $(M+H)^+$: m/z = 317.1; found 317.1.

Step 4: (2S)-1-[(2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-4-yl)methyl]piperidine-2-carboxylic acid



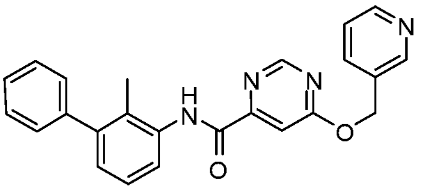
This compound was prepared using a similar procedure as described for Example 1, Step 5, with 4-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide replacing 5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{26}H_{28}N_3O_3$ $(M+H)^+$: m/z = 430.2; found 430.2.

Example 23: 4-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

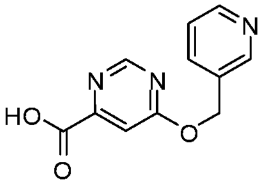


This compound was prepared using a similar procedure as described for Example 4 with 4-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide (Example 25, Step 3) replacing 5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product, which was concentrated and further purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{22}H_{24}N_3O_2$ $(M+H)^+$: m/z = 362.2; found 362.2.

Example 24: N-(2-methylbiphenyl-3-yl)-6-(pyridin-3-ylmethoxy)pyrimidine-4-carboxamide

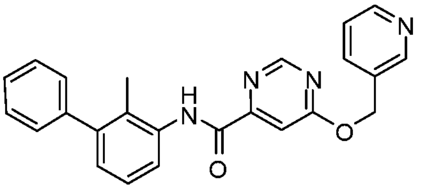


Step 1: 6-(pyridin-3-ylmethoxy)pyrimidine-4-carboxylic acid



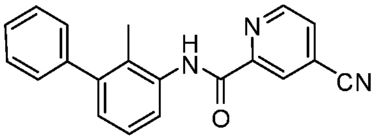
Nicotinyl alcohol (73 μL, 0.76 mmol) was added to a suspension of sodium hydride (20 mg, 0.9 mmol) at rt, and the mixture was allowed to stir at rt for 1h. Then a THF (1mL) solution of 6-chloropyrimidine-4-carboxylic acid (Matrix Scientific cat#073471, 50 mg, 0.3 mmol) was added to the mixture, which was allowed to stir at rt for 3 h. The reaction was quenched with water and 1N HCl, the mixture was extracted with DCM/iPrOH. The organic layer was dried and concentrated to afford product which was used in the next step without further purification. LC-MS calculated for $C_{11}H_{10}N_3O_3$ $(M+H)^+$: m/z = 232.1; found 232.2.

Step 2: N-(2-methylbiphenyl-3-yl)-6-(pyridin-3-ylmethoxy)pyrimidine-4-carboxamide



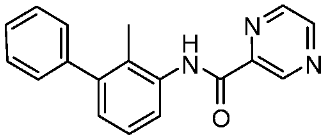
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 6-(pyridin-3-ylmethoxy)pyrimidine-4-carboxylic acid replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{24}H_{21}N_4O_2$ $(M+H)^+$: m/z = 397.2; found 397.1.

Example 25: 4-cyano-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



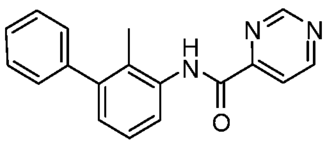
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 4-cyanopyridine-2-carboxylic acid (Bionet Intermediates, cat#BB-0608) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{20}H_{16}N_3O$ $(M+H)^+$: m/z = 314.1; found 314.1.

Example 26: N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide



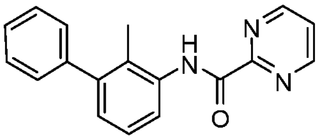
This compound was prepared using a similar procedure as described for Example 1, Step 2, with 2-pyrazinecarboxylic acid (Sigma-Aldrich, cat#P56100) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{18}H_{16}N_3O$ $(M+H)^+$: m/z = 290.1; found 290.2.

Example 27: N-(2-methylbiphenyl-3-yl)pyrimidine-4-carboxamide



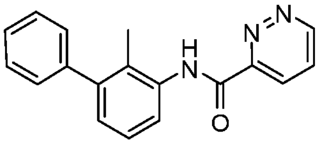
This compound was prepared using a similar procedure as described for Example 1, Step 2, with pyrimidine-4-carboxylic acid (VWR International, cat#101390) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{18}H_{16}N_3O$ $(M+H)^+$: m/z = 290.1; found 290.2.

Example 28: N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide



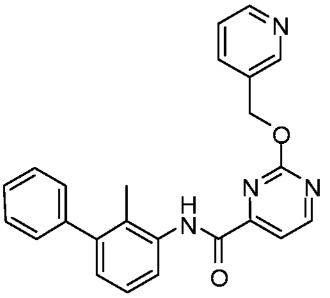
This compound was prepared using a similar procedure as described for Example 1, Step 2, with pyrimidine-2-carboxylic acid (Ark Pham, cat#AK-24353) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{18}H_{16}N_3O$ $(M+H)^+$: m/z = 290.1; found 290.2.

Example 29: N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide

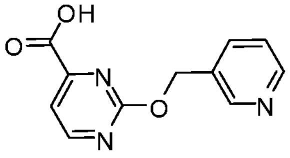


This compound was prepared using a similar procedure as described for Example 1, Step 2, with pyridazine-3-carboxylic acid (Ark Pham, cat#AK-28139) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{18}H_{16}N_3O$ $(M+H)^+$: m/z = 290.1; found 290.1.

Example 30: N-(2-methylbiphenyl-3-yl)-2-(pyridin-3-ylmethoxy)pyrimidine-4-carboxamide

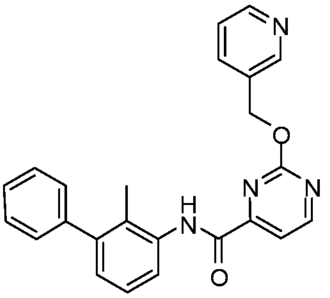


Step 1: 2-(pyridin-3-ylmethoxy)pyrimidine-4-carboxylic acid



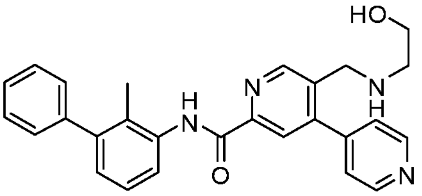
Sodium hydride (20 mg, 0.9 mmol) was added to a tetrahydrofuran (2 mL, 20 mmol) solution of 2-chloropyrimidine-4-carboxylic acid (Ark Pharm, cat#AK-28365, 50 mg, 0.3 mmol) and nicotinyl alcohol (73 µL, 0.76 mmol), which was allowed to stir at 70 °C for 1h to reach full conversion. The reaction mixture was quenched with water and extracted with DCM/iPrOH, and the organic layer was dried and concentrated to afford the desired product. Then the residue was used in the next step without further purification. LC-MS calculated for $C_{11}H_{10}N_3O_3$ $(M+H)^+$: m/z = 232.1; found: 232.1.

Step 2: N-(2-methylbiphenyl-3-yl)-2-(pyridin-3-ylmethoxy)pyrimidine-4-carboxamide

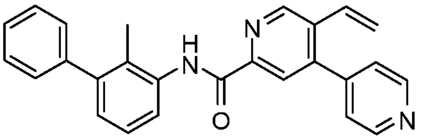


This compound was prepared using a similar procedure as described for Example 1, Step 2, with 2-(pyridin-3-ylmethoxy)pyrimidine-4-carboxylic acid replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{24}H_{21}N_4O_2$ $(M+H)^+$: m/z = 397.2; found 397.2.

Example 31: 5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4,4'-bipyridine-2-carboxamide

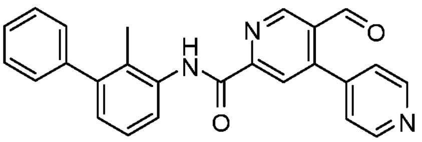


Step 1: N-(2-methylbiphenyl-3-yl)-5-vinyl-4,4'-bipyridine-2-carboxamide



A mixture of *5-bromo-4-chloro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* (*Example 18, Step 1*, 50 mg, 0.1 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (20 µL, 0.1 mmol), and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (6 mg, 0.008 mmol) in 1,4-dioxane (0.9 mL) and water (0.3 mL) was degassed and sealed. It was stirred at 90 °C for 1h to reach full conversion. The reaction mixture was cooled and concentrated, followed by addition of 4-pyridinylboronic acid (30 mg, 0.2 mmol), cesium carbonate (100 mg, 0.4 mmol) and dichloro[1,1'-bis(dicyclohexylphosphino)ferrocene]palladium(II) (*Pd-127*: 9 mg, 0.01 mmol), tert-butyl alcohol (1 mL), and water (0.5 mL). The mixture was degassed with N_2 and heated at 100 °C for 2h. After cooling to rt, the mixture was purified by 0 to 40% EtOAc in DCM. LC-MS calculated for $C_{26}H_{22}N_3O$ $(M+H)^+$: m/z = 392.2; found: 392.1.

Step 2: 5-formyl-N-(2-methylbiphenyl-3-yl)-4,4'-bipyridine-2-carboxamide



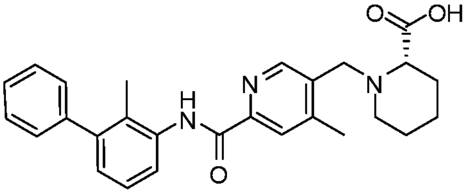
This compound was prepared using a similar procedure as described for *Example 3, Step 3* with *N-(2-methylbiphenyl-3-yl)-5-vinyl-4,4'-bipyridine-2-carboxamide* replacing *3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide*. LC-MS calculated for $C_{25}H_{20}N_3O_2$ $(M+H)^+$: m/z = 394.2; found 394.1.

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

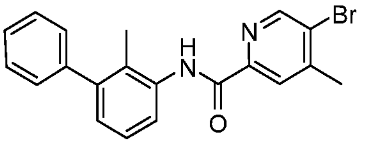
This compound was prepared using a similar procedure as described for *Example 4* with *5-formyl-N-(2-methylbiphenyl-3-yl)-4,4'-bipyridine-2-carboxamide (Step 2)* replacing *5-*

formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product, which was concentrated and further purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{27}H_{27}N_4O_2$ $(M+H)^+$: m/z = 439.2; found 439.2.

Example 32: (2S)-1-[(4-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid

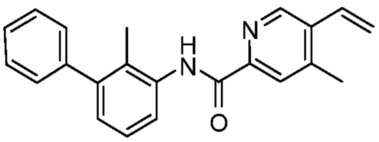


Step 1: 5-bromo-4-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



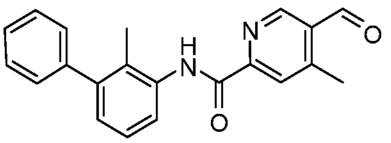
This compound was prepared using a similar procedure as described for *Example 1, Step 2* with 5-bromo-4-methylpyridine-2-carboxylic acid (*Ark Pharm, cat#AK-37510*) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{20}H_{18}BrN_2O$ $(M+H)^+$: m/z = 381.0; found 381.0.

Step 2: 4-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



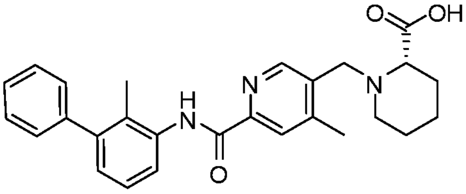
This compound was prepared using a similar procedure as described for *Example 3, Step 2* with *5-bromo-4-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* replacing *5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. LC-MS calculated for $C_{22}H_{21}N_2O$ $(M+H)^+$: m/z = 329.2; found 329.1.

Step 3: 5-formyl-4-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



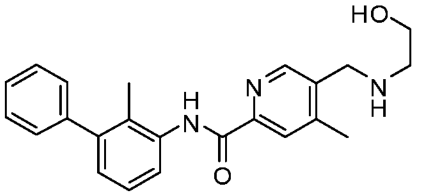
This compound was prepared using a similar procedure as described for *Example 3, Step 3* with *4-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide* replacing *3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide.* LC-MS calculated for $C_{21}H_{19}N_2O_2$ $(M+H)^+$: m/z = 331.1; found 331.1.

Step 4: (2S)-1-[(4-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid



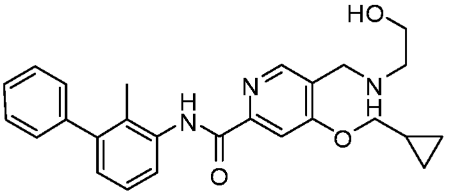
This compound was prepared using a similar procedure as described for *Example 1, Step 5* with *5-formyl-4-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* replacing *5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide.* The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{27}H_{30}N_3O_3$ $(M+H)^+$: m/z = 444.2; found 444.2.

Example 33: 5-{[(2-hydroxyethyl)amino]methyl}-4-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

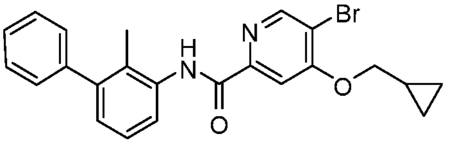


This compound was prepared using a similar procedure as described for *Example 4* with *5-formyl-4-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* (*Example 32, Step 3*) replacing *5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{23}H_{26}N_3O_2$ $(M+H)^+$: m/z = 376.2; found 376.2.

Example 34: 4-(cyclopropylmethoxy)-5-((2-hydroxyethylamino)methyl)-N-(2-methylbiphenyl-3-yl)picolinamide

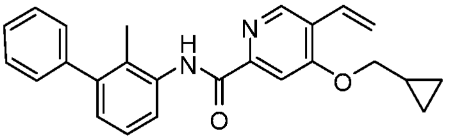


Step 1: 5-bromo-4-(cyclopropylmethoxy)-N-(2-methylbiphenyl-3-yl)picolinamide



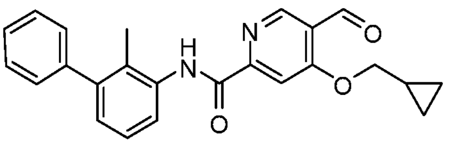
This compound was prepared using a similar procedure as described for *Example 18, Step 2* with cyclopropylmethanol replacing 3-(hydroxymethyl)benzonitrile. LC-MS calculated for $C_{23}H_{22}BrN_2O_2$ $(M+H)^+$: m/z = 437.1; found 437.1.

Step 2: 4-(cyclopropylmethoxy)-N-(2-methylbiphenyl-3-yl)-5-vinylpicolinamide



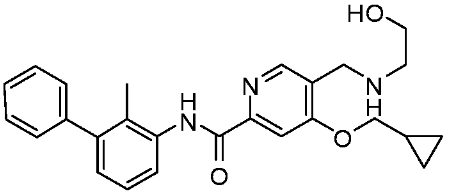
This compound was prepared using a similar procedure as described for *Example 3, Step 2* with *5-bromo-4-(cyclopropylmethoxy)-N-(2-methylbiphenyl-3-yl)picolinamide* replacing *5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. LC-MS calculated for $C_{25}H_{24}N_2O_2$ $(M+H)^+$: m/z = 385.2; found 385.2.

Step 3: 4-(cyclopropylmethoxy)-5-formyl-N-(2-methylbiphenyl-3-yl)picolinamide



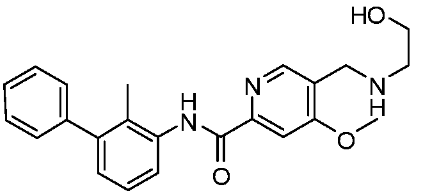
This compound was prepared using a similar procedure as described for *Example 3, Step 3* with *4-(cyclopropylmethoxy)-N-(2-methylbiphenyl-3-yl)-5-vinylpicolinamide* replacing *3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide*. LC-MS calculated for $C_{24}H_{23}N_2O_3$ $(M+H)^+$: m/z = 387.2; found 387.2.

Step 4: 4-(cyclopropylmethoxy)-5-((2-hydroxyethylamino)methyl)-N-(2-methylbiphenyl-3-yl)picolinamide

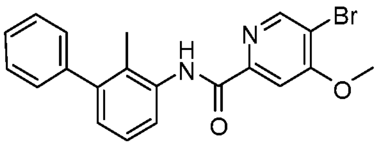


This compound was prepared using a similar procedure as described for *Example 4* with *4-(cyclopropylmethoxy)-5-formyl-N-(2-methylbiphenyl-3-yl)picolinamide* replacing *5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{26}H_{30}N_3O_3$ $(M+H)^+$: m/z = 432.2; found 432.2.

Example 35: 5-{[(2-hydroxyethyl)amino]methyl}-4-methoxy-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

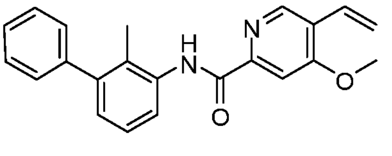


Step 1: 5-bromo-4-methoxy-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



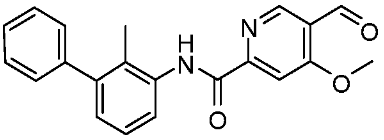
Mixture of sodium methoxide (80 μL, 0.4 mmol) was added to *5-bromo-4-chloro-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* (*Example 18, Step 1*, 50 mg, 0.1 mmol) at rt. Then the mixture was allowed to stir at rt for 4h to reach full conversion. The reaction was quenched with water and extracted with EtOAc, and the organic layer was dried and concentrated to afford desired product which was used for next step without further purification. LC-MS calculated for $C_{20}H_{18}BrN_2O_2$ $(M+H)^+$: m/z = 397.0; found 397.0.

Step 2: 4-methoxy-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide



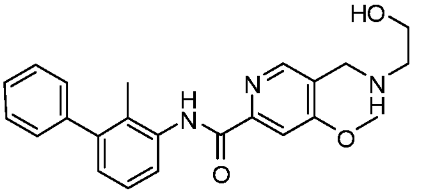
This compound was prepared using a similar procedure as described for *Example 3, Step 2* with *5-bromo-4-methoxy-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* replacing *5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide.* LC-MS calculated for $C_{22}H_{21}N_2O_2$ $(M+H)^+$: m/z = 345.2; found 345.1.

Step 3: 5-formyl-4-methoxy-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



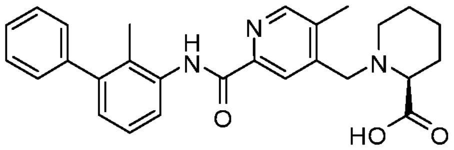
This compound was prepared using a similar procedure as described for *Example 3, Step 3* with *4-methoxy-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide* replacing *3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide.* LC-MS calculated for $C_{21}H_{19}N_2O_3$ $(M+H)^+$: m/z = 347.1; found 347.1.

Step 4: 5-{[(2-hydroxyethyl)amino]methyl}-4-methoxy-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

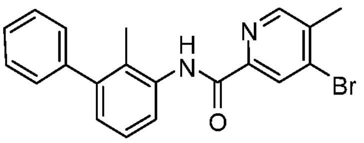


This compound was prepared using a similar procedure as described for *Example 4* with *5-formyl-4-methoxy-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* replacing *5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide.* The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{23}H_{26}N_3O_3$ $(M+H)^+$: m/z = 392.2; found 392.2.

Example 36: (2S)-1-[(5-methyl-2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-4-yl)methyl]piperidine-2-carboxylic acid

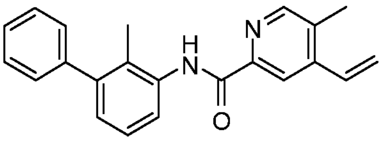


Step 1: 4-bromo-5-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



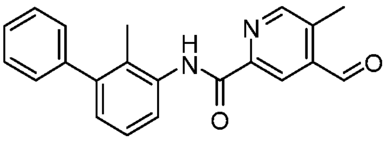
This compound was prepared using a similar procedure as described for *Example 1, Step 2* with 4-bromo-5-methylpyridine-2-carboxylic acid (*Ark Pharm, cat#AK-37510*) replacing 5-(methoxycarbonyl)pyridine-2-carboxylic acid. LC-MS calculated for $C_{20}H_{18}BrN_2O$ $(M+H)^+$: m/z = 381.0; found 381.0.

Step 2: 5-methyl-N-(2-methylbiphenyl-3-yl)-4-vinylpyridine-2-carboxamide



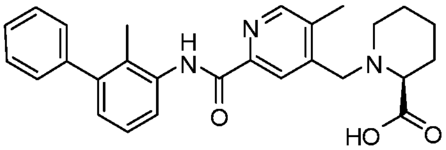
This compound was prepared using a similar procedure as described for *Example 3, Step 2* with *4-bromo-5-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* replacing *5-bromo-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. LC-MS calculated for $C_{22}H_{21}N_2O$ $(M+H)^+$: m/z = 329.1; found 329.2.

Step 3: 4-formyl-5-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide



This compound was prepared using a similar procedure as described for *Example 3, Step 3* with *5-methyl-N-(2-methylbiphenyl-3-yl)-4-vinylpyridine-2-carboxamide* replacing *3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide*. LC-MS calculated for $C_{21}H_{19}N_2O_2$ $(M+H)^+$: m/z = 331.1; found 331.1.

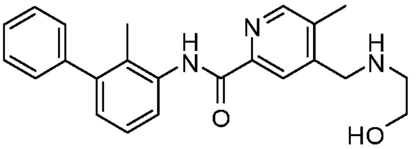
Step 4: (2S)-1-[(5-methyl-2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-4-yl)methyl]piperidine-2-carboxylic acid



This compound was prepared using a similar procedure as described for *Example 1, Step 5* with *4-formyl-5-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* replacing

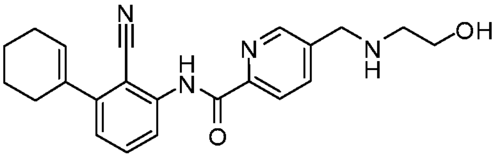
5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{27}H_{30}N_3O_3$ $(M+H)^+$: m/z = 444.2; found 444.2.

Example 37: 4-{[(2-hydroxyethyl)amino]methyl}-5-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide

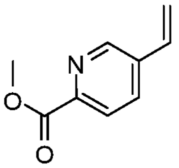


This compound was prepared using a similar procedure as described for *Example 4* with *4-formyl-5-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide* (*Example 36, Step 3*) replacing *5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{23}H_{26}N_3O_2$ $(M+H)^+$: m/z = 376.2; found 376.2.

Example 38: N-(2-cyano-3-cyclohex-1-en-1-ylphenyl)-5-{[(2-hydroxyethyl)amino]methyl} pyridine-2-carboxamide

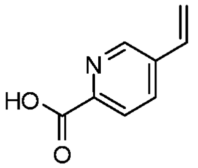


Step 1: methyl 5-vinylpyridine-2-carboxylate



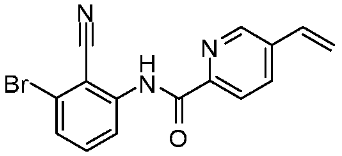
Sodium carbonate (1200 mg, 12 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane [$PdCl_2$(dppf), 100 mg, 0.1 mmol], 1,4-dioxane (15 mL), water (3 mL), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (628 μL, 3.70 mmol) were added to 5-bromopyridine-2-carboxylic acid methyl ester (*Combi-Blocks, cat#CA-4117*, 800 mg, 4 mmol), and degased with N_2. The mixture was heated at 90 °C for 2h to reach full conversion. The mixture was purified with 0 to 35% EtOAc in Hexanes to afford the desired product as a white solid.

Step 2: 5-vinylpyridine-2-carboxylic acid



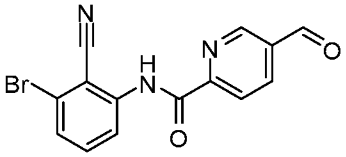
3 mL 1M NaOH solution (3 mmol) was added to *methyl 5-vinylpyridine-2-carboxylate* and heated at 45°C for 2h to reach full conversion. The mixture was concentrated to afford desired product as a white solid, which was used for next step without further purification.

Step 3: N-(3-bromo-2-cyanophenyl)-5-vinylpyridine-2-carboxamide



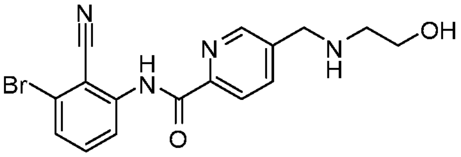
2.0 M oxalyl chloride in DCM (4.7 mL, 9.3 mmol), N,N-dimethylformamide (30 µL, 0.3 mmol) was added to 5-vinylpyridine-2-carboxylic acid (522 mg, 3.50 mmol) under N_2 at 0 °C. The mixture was allowed to stir at rt for 2h, then the mixture was concentrated under reduced pressure and the residue was used for next step without further purification. 2-amino-6-bromobenzonitrile (*Ark Pharm, AK-36350* , 690 mg, 3.5 mmol) and methylene chloride (10 mL) were added to the residue, followed by addition of triethylamine (1000 µL, 10 mmol) at 0 °C drop-wise. The mixture was allowed to stir at rt for 1h to reach full conversion. The mixture was concentrated and purified by 0 to 50% EtOAc in Hex. LC-MS calculated for $C_{15}H_{11}BrN_3O$ $(M+H)^+$: m/z = 328.0; found 328.0.

Step 4: N-(3-bromo-2-cyanophenyl)-5-formylpyridine-2-carboxamide



This compound was prepared using a similar procedure as described for *Example 3, Step 3* with *N-(3-bromo-2-cyanophenyl)-5-vinylpyridine-2-carboxamide* replacing *3-methyl-N-(2-methylbiphenyl-3-yl)-5-vinylpyridine-2-carboxamide*. LC-MS calculated for $C_{14}H_9BrN_3O_2$ $(M+H)^+$: m/z = 329.0; found 329.0.

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

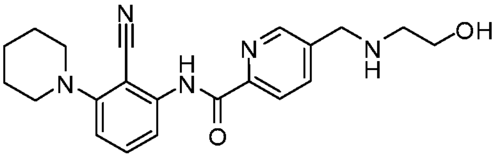


This compound was prepared using a similar procedure as described for *Example 4* with *N-(3-bromo-2-cyanophenyl)-5-formylpyridine-2-carboxamide* replacing *5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. The reaction mixture was purified by 0 to 12% MeOH in DCM to give the desired product. LC-MS calculated for $C_{16}H_{16}BrN_4O_2$ $(M+H)^+$: m/z = 375.0; found 375.0.

Step 6: N-(2-cyano-3-cyclohex-1-en-1-ylphenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide

A mixture of *N-(3-bromo-2-cyanophenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide* (10 mg, 0.03 mmol), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with DCM (1 mg, 0.002 mmol), sodium carbonate (10 mg), and 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.66 mg, 0.0320 mmol) in 1,4-dioxane (0.2 mL) and water (0.07 mL) was degassed with N_2 and sealed. It was stirred at 95°C for 2h to reach full conversion. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{22}H_{25}N_4O_2$ $(M+H)^+$: m/z = 377.2; found 377.1.

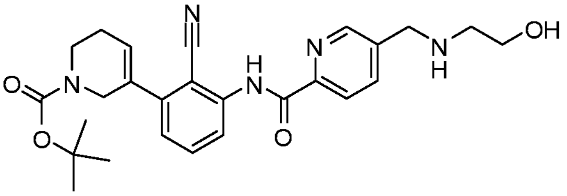
Example 39: N-(2-cyano-3-piperidin-1-ylphenyl)-5-{[(2-hydroxyethyl)amino]methyl} pyridine-2-carboxamide



A stirred mixture of piperidine (10 μL, 0.1 mmol), *N-(3-bromo-2-cyanophenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide* (*Example 38, Step 5*, 11.2 mg, 0.03 mmol), (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphoranyl]palladium (2.28 mg, 0.003 mmol), and sodium tert-butoxide (20 mg, 0.2 mmol) in 1,4-dioxane (0.083 mL) was heated at 110 °C for 2 h to reach full conversion. The volatiles were removed and the residue was purified by prep-HPLC (pH = 2, acetonitrile/

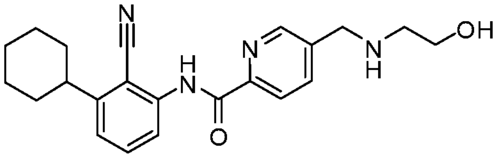
water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{21}H_{26}N_5O_2$ $(M+H)^+$: m/z = 380.2; found 380.2.

Example 40: tert-butyl 5-(2-cyano-3-{[(5-{[(2-hydroxyethyl)amino]methyl}pyridin-2-yl)carbonyl]amino}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate

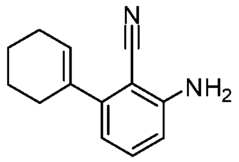


This compound was prepared using a similar procedure as described for *Example 38, Step 6* with tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (*Combi-Blocks, cat# FM-2863*) replacing 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The volatiles were removed and the residue was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{26}H_{32}N_5O_4$ $(M+H)^+$: m/z = 478.2; found 478.2.

Example 41: N-(2-cyano-3-cyclohexylphenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide

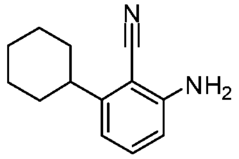


Step 1: 2-amino-6-cyclohex-1-en-1-ylbenzonitrile



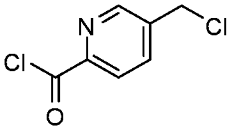
This compound was prepared using a similar procedure as described for *Example 1, Step 1* with 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane replacing phenylboronic acid, and with 2-amino-6-bromobenzonitrile (*Astatech, cat#CL8148*) replacing 3-bromo-2-methylaniline. LC-MS calculated for $C_{13}H_{15}N_2$ $(M+H)^+$: m/z = 199.1; found 199.1.

Step 2: 2-amino-6-cyclohexylbenzonitrile



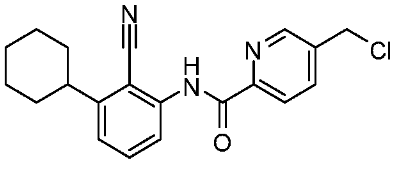
A mixture of *2-amino-6-cyclohex-1-en-1-ylbenzonitrile* (100 mg, 0.5 mmol) and 10% Pd/C (53 mg, 0.050 mmol) in methanol (5 mL) was stirred under an atmosphere of H_2 at room temperature for 3h to reach full conversion. The mixture was filtered through silica gel and concentrated and used for next step without further purification. LC-MS calculated for $C_{13}H_{17}N_2$ $(M+H)^+$: m/z = 201.1; found 201.1.

Step 3: 5-(chloromethyl)picolinoyl chloride



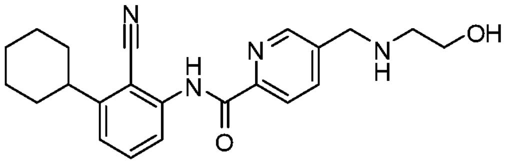
1N NaOH solution was added to a THF (1mL) solution of methyl 5-(bromomethyl) pyridine-2-carboxylate (*Ark Pharm, cat#AK153186*, 20 mg, 0.08 mmol) and the mixture was allowed to stir at rt for 1h. The mixture was acidified with 1N HCl solution until pH = 4, and then the mixture was extracted with DCM. The organic layers were combined, dried and concentrated. To the residue was added 2.0 M oxalyl chloride in DCM (0.10 mL, 0.20 mmol) and N,N-dimethylformamide (0.6 µL, 0.008 mmol) at 0 °C under N_2. The mixture was allowed to stir at rt for 2h, and then the mixture was concentrated and the residue was used for next step without further purification.

Step 4: 5-(chloromethyl)-N-(2-cyano-3-cyclohexylphenyl)pyridine-2-carboxamide



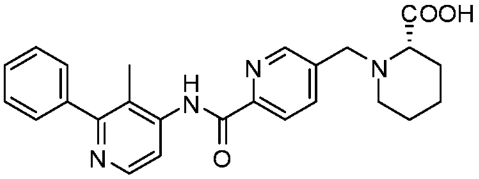
The DCM (1mL) solution of crude *5-(chloromethyl)picolinoyl chloride* was added to a DCM (1mL) solution of *2-amino-6-cyclohexylbenzonitrile* (20 mg, 0.1 mmol) and triethylamine (30 µL, 0.2 mmol) at 0 °C drop-wise. The mixture was allowed to stir at rt for 2h to reach full conversion. The mixture was concentrated and used for next step without further purification. LC-MS calculated for $C_{20}H_{21}ClN_3O$ $(M+H)^+$: m/z = 354.1; found 354.1.

Step 5: N-(2-cyano-3-cyclohexylphenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide

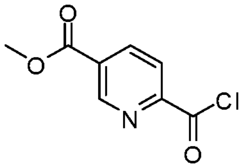


A mixture of *5-(chloromethyl)-N-(2-cyano-3-cyclohexylphenyl)pyridine-2-carboxamide* (40 mg, 0.1 mmol), ethanolamine (10 µL, 0.2 mmol) and potassium carbonate (41 mg, 0.30 mmol) in N,N-dimethylformamide (0.3 mL, 4 mmol) was stirred at rt for overnight. The mixture was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{22}H_{27}N_4O_2$ $(M+H)^+$: m/z = 379.2; found 379.2.

Example 42: (S)-1-((6-(3-methyl-2-phenylpyridin-4-ylcarbamoyl)pyridin-3-yl)methyl)piperidine-2-carboxylic acid

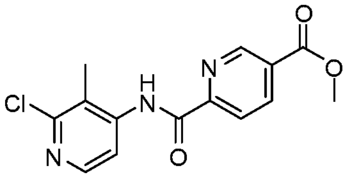


Step 1: methyl 6-(chlorocarbonyl)nicotinate



This compound was prepared using a similar procedure as described for *Example 41, Step 3* with 5-(methoxycarbonyl)pyridine-2-carboxylic acid (*Oakwood Chemical, cat#017196*) replacing methyl 5-(bromomethyl) pyridine-2-carboxylate.

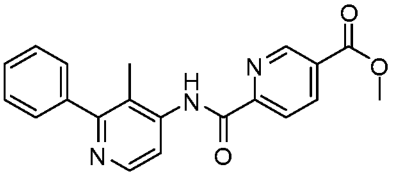
Step 2: methyl 6-{[(2-chloro-3-methylpyridin-4-yl)amino]carbonyl}nicotinate



This compound was prepared using a similar procedure as described for *Example 41, Step 4* with 2-chloro-3-methylpyridin-4-amine (*Astatech, cat#25664*) replacing *2-amino-6-*

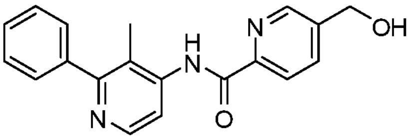
cyclohexylbenzonitrile, and with *methyl 6-(chlorocarbonyl)nicotinate* replacing *5-(chloromethyl)picolinoyl chloride*. LC-MS calculated for $C_{14}H_{13}ClN_3O_3$ $(M+H)^+$: m/z = 306.1; found 306.1.

Step 3: methyl 6-{[(3-methyl-2-phenylpyridin-4-yl)amino]carbonyl}nicotinate



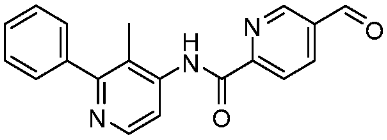
Pd-127 (40 mg, 0.06 mmol) was added to the mixture of *methyl 6-{[(2-chloro-3-methylpyridin-4-yl)amino]carbonyl}nicotinate* (200 mg, 0.6 mmol), phenylboronic acid (132 mg, 1.08 mmol) and cesium carbonate (400 mg, 1 mmol) in 1,4-dioxane (3.69 mL) and water (216 µL). The mixture was stirred at 90 °C for 1 h. After concentration, the mixture was purified by 0 to 50% EtOAc in hexanes to afford the desired product. LC-MS calculated for $C_{20}H_{18}N_3O_3$ $(M+H)^+$: m/z = 348.1; found 348.1.

Step 4: 5-(hydroxymethyl)-N-(3-methyl-2-phenylpyridin-4-yl)pyridine-2-carboxamide



This compound was prepared using a similar procedure as described for *Example 1, Step 3* with *methyl 6-{[(3-methyl-2-phenylpyridin-4-yl)amino]carbonyl}nicotinate* replacing *methyl 6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}nicotinate*. LC-MS calculated for $C_{19}H_{18}N_3O_2$ $(M+H)^+$: m/z = 320.1; found 320.1.

Step 5: 5-formyl-N-(3-methyl-2-phenylpyridin-4-yl)pyridine-2-carboxamide

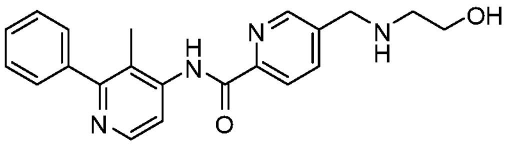


This compound was prepared using a similar procedure as described for *Example 1, Step 4* with *5-(hydroxymethyl)-N-(3-methyl-2-phenylpyridin-4-yl)pyridine-2-carboxamide* replacing *5-(hydroxymethyl)-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamid*. LC-MS calculated for $C_{19}H_{16}N_3O_2$ $(M+H)^+$: m/z = 318.1; found 318.1.

Step 6: (S)-1-((6-(3-methyl-2-phenylpyridin-4-ylcarbamoyl)pyridin-3-yl)methyl)piperidine-2-carboxylic acid

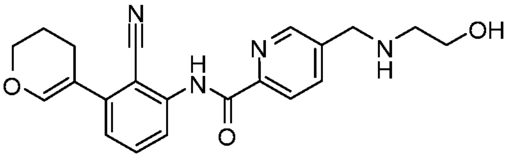
This compound was prepared using a similar procedure as described for *Example 1, Step 5* with *5-formyl-N-(3-methyl-2-phenylpyridin-4-yl)pyridine-2-carboxamide* replacing *5-formyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{25}H_{27}N_4O_3$ $(M+H)^+$: m/z = 431.2; found 431.2.

Example 43: 5-{[(2-hydroxyethyl)amino]methyl}-N-(3-methyl-2-phenylpyridin-4-yl)pyridine-2-carboxamide



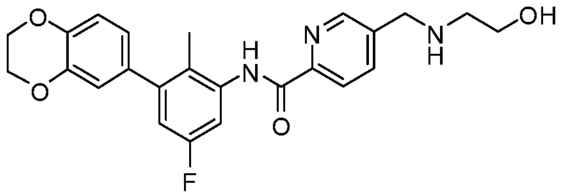
This compound was prepared using a similar procedure as described for *Example 4* with *5-formyl-N-(3-methyl-2-phenylpyridin-4-yl)pyridine-2-carboxamide (Example 42, Step 5)* replacing *5-formyl-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide*. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{21}H_{23}N_4O_2$ $(M+H)^+$: m/z = 363.1; found 363.2.

Example 44: N-[2-cyano-3-(3,4-dihydro-2H-pyran-5-yl)phenyl]-5-{[(2-hydroxyethyl)amino] methyl}pyridine-2-carboxamide

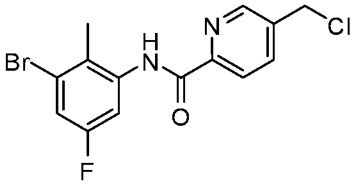


This compound was prepared using a similar procedure as described for *Example 38, Step 6* with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-pyran (*Combi-Blocks, cat# PN-6040*) replacing 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The volatiles were removed, and the residue was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{21}H_{23}N_4O_3$ $(M+H)^+$: m/z = 379.2; found 379.2.

Example 45: N-[3-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-fluoro-2-methylphenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide

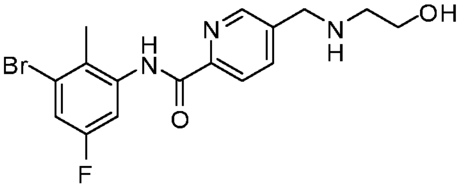


Step 1: N-(3-bromo-5-fluoro-2-methylphenyl)-5-(chloromethyl)pyridine-2-carboxamide



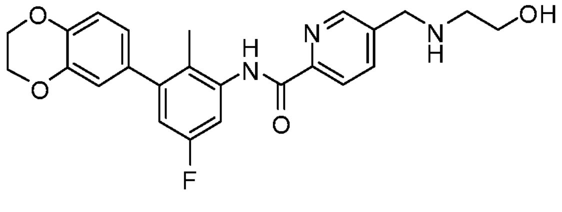
This compound was prepared using a similar procedure as described for *Example 41, Step 4* with 3-bromo-5-fluoro-2-methylaniline (*Combi-Blocks, cat# ST-8934*) replacing *2-amino-6-cyclohexylbenzonitrile.*

Step 2: N-(3-bromo-5-fluoro-2-methylphenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide



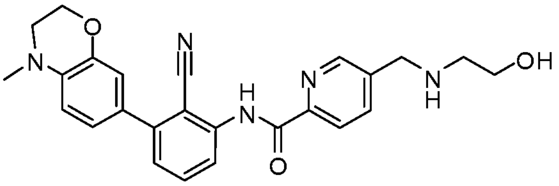
This compound was prepared using a similar procedure as described for *Example 41, Step 5* with *N-(3-bromo-5-fluoro-2-methylphenyl)-5-(chloromethyl)pyridine-2-carboxamide* replacing *5-(chloromethyl)-N-(2-cyano-3-cyclohexylphenyl)pyridine-2-carboxamide.* LC-MS calculated for $C_{16}H_{18}BrFN_3O_2$ $(M+H)^+$: m/z = 382.1; found 382.0.

Step 3: N-[3-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-fluoro-2-methylphenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide



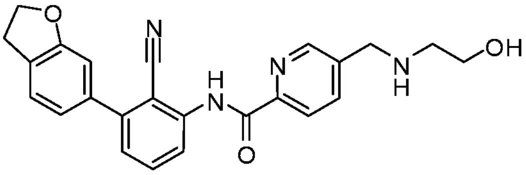
This compound was prepared using a similar procedure as described for *Example 38, Step 6* with 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (*Sigma-Aldrich, cat#635995*) replacing 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and with *N-(3-bromo-5-fluoro-2-methylphenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide* replacing *N-(3-bromo-2-cyanophenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide*. The volatiles were removed, and the residue was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{24}H_{25}FN_3O_4$ $(M+H)^+$: m/z = 438.2; found 438.1.

Example 46: N-[2-cyano-3-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide



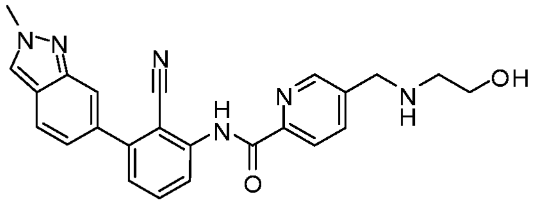
This compound was prepared using a similar procedure as described for *Example 38, Step 6* with 4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-1,4-benzoxazine (*Maybridge Building Blocks, cat# CC13539*) replacing 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The volatiles were removed and the residue was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{25}H_{26}N_5O_3$ $(M+H)^+$: m/z = 444.2; found 444.2.

Example 47: N-[2-cyano-3-(2,3-dihydro-1-benzofuran-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide



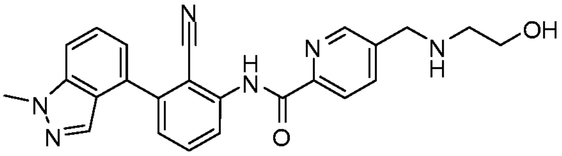
This compound was prepared using a similar procedure as described for *Example 38, Step 6* with (2,3-dihydrobenzofuran-6-yl)boronic acid (*Ark Pharm, cat# AK143637*) replacing 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The volatiles were removed and the residue was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{24}H_{23}N_4O_3$ $(M+H)^+$: m/z = 415.2; found 415.2.

Example 48: N-[2-cyano-3-(2-methyl-2H-indazol-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide



This compound was prepared using a similar procedure as described for *Example 38, Step 6* with 2-methylindazole-6-boronic acid pinacol ester (*Combi-Blocks, cat# PN-9131*) replacing 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The volatiles were removed and the residue was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{24}H_{23}N_6O_2$ $(M+H)^+$: m/z = 427.2; found 427.2.

Example 49: N-[2-cyano-3-(1-methyl-1H-indazol-4-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide



This compound was prepared using a similar procedure as described for *Example 38, Step 6* with 1-methyl-1H-indazole-4-boronic acid pinacol ester (*Aldrich, cat# 725323*) replacing 2-cyclohex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The volatiles were removed, and the residue was purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as its TFA salt. LC-MS calculated for $C_{24}H_{23}N_6O_2$ $(M+H)^+$: m/z = 427.2; found 427.2.

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 (665 nm/620 nm 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: + = $IC_{50} \leq 10$ nM; ++ = 10 nM < $IC_{50} \leq 100$ nM; +++ = 100 nM < $IC_{50} \leq 1000$ nM; ++++ = $IC_{50} > 1000$ 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

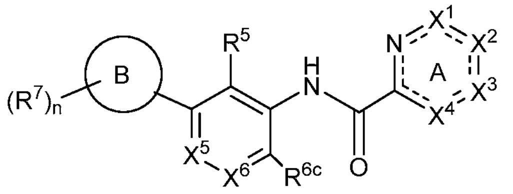
Example	PD-1/PD-L1 HTRF IC_{50} (nM)
1	++
2	++
3	+++
4	++
5	+++
6	++
7	++
8	+
9	++
10	+
11	++
12	++
13	+++
14	++
15	+++
16	++
17	++
18	++
19	++
20	++
21	+++

Example	**PD-1/PD-L1 HTRF IC_{50} (nM)**
23	++
24	+++
25	++
26	++
27	++
28	+++
29	+++
30	+++
31	++
32	+
33	+
34	++
35	+
36	++
37	++
38	+
39	++++
40	+++
41	++
42	++++
43	+++
44	++
45	+
46	+++
47	++
48	++
49	+

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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is N or CR^{6b};

ring B is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, provided ring B is other than 9-H-carbazol-4-yl, 2,3,4,9-tetrahydro-1H-carbazol-5-yl or 1H-tetrazolyl;

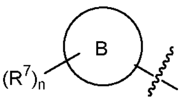
R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} 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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 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}S(O)R^{11}, NR^{11}S(O)$_2$R^{11}, NR^{11}S(O)$_2$NR^{11}R^{11}, S(O)R^{11}, S(O)NR^{11}R^{11}, S(O)$_2$R^{11}, and S(O)$_2$NR^{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^5 are each optionally substituted with 1, 2 or 3 R^b substituents; wherein R^5 is other than F when ring B is C$_{3-10}$ cycloalkyl, 5- to 14-membered heteroaryl or 4- to 10-membered heterocycloalkyl;

each R^{11} is independently selected from H, CN, C$_{1-6}$ alkyl, C$_{1-4}$ haloalkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ 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$_{6-1 0}$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 R^b substituents;

R^{6a}, R^{6b} and R^{6c} 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)$_2$R^{10}, NR^{10}S(O)$_2$NR^{10}R^{10}, S(O)R^{10}, S(O)NR^{10}R^{10}, S(O)$_2$R^{10}, and S(O)$_2$NR^{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$_{2-4}$ 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- of R^{6a}, R^{6b}, R^{6c} and R^{10} are each optionally substituted with 1, 2 or 3 independently selected R^d substituents;

or two adjacent R^7 substituents, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 4- to 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 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- to 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-10} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents, provided 

is other than 9-H-carbazol-4-yl or 2,3,4,9-tetrahydro-1H-carbazol-5-yl, each of which is optionally substituted by 1, 2 or 3 independently selected R^b substituents;

or two R^7 substituents attached to the same ring carbon atom of ring B, together with the carbon atom to which they are attached, form a 4- to 7-membered heterocycloalkyl ring having 1-4 heteroatoms as ring members selected from N, O and S or a C_{3-6} cycloalkyl ring, wherein the 4- to 7-membered heterocycloalkyl ring and C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^1 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^2 and X^1 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^2 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^3 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^3 and X^4 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

or R^4 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d 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^b substituent is independently selected from halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} 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, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, 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_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} 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^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 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, and S(O)$_2$NR^{g}R^g; wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 3, 4, or 5 R^n substituents independently selected from C_{1-4} alkyl, 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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, halo, CN, R^o, NHOR^o, OR^o, SR^o, C(O)R^o, C(O)NR^{o}R^o, C(O)OR^o, OC(O)R^o, OC(O)NR^{o}R^o, NHR^o, NR^{o}R^o, NR^{o}C(O)R^o, NR^{o}C(O)NR^{o}R^o, NR^{o}C(O)OR^o, C(=NR^o)NR^{o}R^o, NR^{o}C(=NR^o)NR^{o}R^o, S(O)R^o, S(O)NR^{o}R^o, S(O)$_2$R^o, NR^{o}S(O)$_2$R^o, NR^{o}S(O)$_2$NR^{o}R^o, and S(O)$_2$NR^{o}R^o, wherein the C_{1-4} alkyl, 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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-4} haloalkyl of R^n are each optionally substituted with 1, 2 or 3 R^q substituents;

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} 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^{r}R^r, C(O)OR^r, OC(O)R^r, OC(O)NR^{r}R^r, NHR^r, NR^{r}R^r, NR^{r}C(O)R^r, NR^{r}C(O)NR^{r}R^r, NR^{r}C(O)OR^r, C(=NR^r)NR^{r}R^r, NR^{r}C(=NR^r)NR^{r}R^r, NR^{r}C(=NOH)NR^{r}R^r, NR^{r}C(=NCN)NR^{r}R^r, S(O)R^r, S(O)NR^{r}R^r, S(O)$_2$R^r, NR^{r}S(O)$_2$R^r, NR^{r}S(O)$_2$NR^{r}R^r and S(O)$_2$NR^{r}R^r, wherein the C_{1-6} alkyl,

C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} 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 are each 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_{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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 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, $NR^iC(O)R^i$, $NR^iC(O)NR^iR^i$, $NR^iC(O)OR^i$, $C(=NR^i)NR^iR^i$, $NR^iC(=NR^i)NR^iR^i$, $S(O)R^i$, $S(O)NR^iR^i$, $S(O)_2R^i$, $NR^iS(O)_2R^i$, $NR^iS(O)_2NR^iR^i$, and $S(O)_2NR^iR^i$, wherein the C_{1-6} alkyl, C_{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 further optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} alkyl, 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, 4-7 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-6} alkynyl, 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;

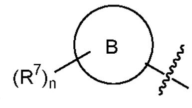
or any two R^o substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents; and

each R^e, R^i, R^k, R^o or R^r is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, 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, and C_{2-4} alkynyl of R^e, 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} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^8, NR^8R^8, and C_{1-4} haloalkoxy, 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, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl and each R^8 is independently C_{1-6} alkyl;

$\overline{\overline{}}$ is a single bond or a double bond, wherein ring A includes at least one double bond;

the subscript n is an integer of 1, 2, 3, 4 or 5; and

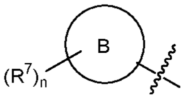
with the proviso (i) when 

is 2,6-dioxohexahydropyrimidin-1-yl, 2-oxopyrrolidin-1-yl, benzo[d]thiazol-2-yl, 2-amino-4-methyl-5,6-dihydro-1,3-thiazin-4-yl, 4-

methyl-6-[4-(morpholine-4-carbonyl)anilino]-5-oxo-pyrazin-2-yl, 5,7-dimethylbenzo[d]oxazol-2-yl, 6-[4-(morpholine-4-carbonyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl, 8-[4-(morpholine-4-carbonyl)anilino]imidazo[1,2-a]pyrazin-6-yl, oxazolo[4,5-b]pyridine-2-yl, or 1-methyl-2-oxo-1,6-naphthridin-3-yl, ring A in Formula (I') is not 2-pyridyl or 2-pyridyl optionally substituted with halo, methylcarboxy, 1,2,4-triazol-4-yl, 1-piperidinyl, or cyclopropyl;

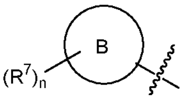
(ii) when ring B is thiazolo[5,4-b]pyridin-2-yl or 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl, ring A in Formula (I') is other than 2-quinolyl;

(iii) when ring B is 1-piperazinyl, ring A in Formula (I') is not 3-(4-benzyloxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl;

(iv) when 

is 6-[1-(dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-4-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl, ring A in Formula (I') is not 1-methylpyrrolo[2,3-b]pyridine-6-yl;

(v) when ring B is 2-oxo-1,2-dihydropyridin-5-yl, 2-oxo-1,2-dihydropyrazin-5-yl or 6-oxo-1H-pyridazin-3-yl, R^2 is other than t-butyl;

(vi) when 

is 3,5-dimethylphenyl, R^5 is other than 4-amino-1-piperidinyl; and

(vii) the compound is other than 6-((2R,6S)-2,6-dimethylmorpholino)-N-(2-methyl-4'-(trifluoromethoxy)biphenyl-3-yl)pyridazine-3-carboxamide or N-(3-(3-acetyl-2-oxoimidazolidin-1-yl)-2-methylphenyl)-5,6,7,8-tetrahydroquinoline-2-carboxamide.

2. The compound of claim 1, 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is N or CR^{6b};

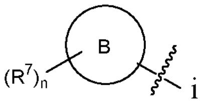
ring B is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, provided ring B is other than 9-H-carbazol-4-yl, 2,3,4,9-tetrahydro-1H-carbazol-5-yl or 1H-tetrazolyl;

R^1, R^2, R^3, R^4 and R^7 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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 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, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$, $C(O)OR^{11}$, $OC(O)R^{11}$, $OC(O)NR^{11}R^{11}$, $NR^{11}C(O)R^{11}$, $NR^{11}C(O)OR^{11}$, $NR^{11}C(O)NR^{11}R^{11}$, $C(=NR^{11})R^{11}$, $C(=NR^{11})NR^{11}R^{11}$, $NR^{11}C(=NR^{11})NR^{11}R^{11}$, $NR^{11}S(O)R^{11}$, $NR^{11}S(O)_2R^{11}$, $NR^{11}S(O)_2NR^{11}R^{11}$, $S(O)R^{11}$, $S(O)NR^{11}R^{11}$, $S(O)_2R^{11}$, and $S(O)_2NR^{11}R^{11}$, 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^5 are each optionally substituted with 1, 2 or 3 R^b substituents; wherein R^5 is other than F when ring B is C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl or 4- to 10-membered heterocycloalkyl;

each R^{11} is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 R^b substituents;

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

or two adjacent R^7 substituents, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 4- to 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 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- to 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-10} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents, provided  is other than 9-H-carbazol-4-yl or 2,3,4,9-tetrahydro-1H-carbazol-5-yl, each of which is optionally substituted by 1 or 2 independently selected R^b substituents;

or two R^7 substituents attached to the same ring carbon atom of ring B, together with the carbon atom to which they are attached, form a 4- to 7-membered heterocycloalkyl ring having 1-4 heteroatoms as ring members selected from N, O and S or a C_{3-6} cycloalkyl ring, wherein the 4- to 7-membered heterocycloalkyl ring and C_{3-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^1 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^1 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^3 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^3 and X^4 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^4 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, 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, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-4} alkyl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl of R^d are each further optionally substituted with 1-3 independently selected R^f substituents;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, 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_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, $NR^gC(O)R^g$, $NR^gC(O)NR^gR^g$, $NR^gC(O)OR^g$, $C(=NR^g)NR^gR^g$, $NR^gC(=NR^g)NR^gR^g$, $S(O)R^g$, $S(O)NR^gR^g$, $S(O)_2R^g$, $NR^gS(O)_2R^g$, $NR^gS(O)_2NR^gR^g$, and $S(O)_2NR^gR^g$; wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 3, 4, or 5 R^n substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, R^o, $NHOR^o$, 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 $S(O)_2NR^oR^o$;

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 independently selected R^p 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_{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_{1-6} haloalkyl, 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^{i}R^i, NR^{i}C(=NR^i)NR^{i}R^i, S(O)R^i, S(O)NR^{i}R^i, S(O)$_2$R^i, NR^{i}S(O)$_2$R^i, NR^{i}S(O)$_2$NR^{i}R^i, and S(O)$_2$NR^{i}R^i, wherein the C$_{1-6}$ alkyl, 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-, and (4-7 membered heterocycloalkyl)-C$_{1-4}$ alkyl- of R^h are each further optionally substituted by 1, 2, or 3 R^j substituents independently selected from C$_{3-6}$ cycloalkyl, C$_{6-10}$ aryl, 5 or 6-membered heteroaryl, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl, halo, C$_{1-4}$ alkyl, C$_{1-4}$ haloalkyl, CN, NHOR^k, OR^k, SR^k, C(O)R^k, C(O)NR^{k}R^k, C(O)OR^k, OC(O)R^k, OC(O)NR^{k}R^k, NHR^k, NR^{k}R^k, NR^{k}C(O)R^k, NR^{k}C(O)NR^{k}R^k, NR^{k}C(O)OR^k, C(=NR^k)NR^{k}R^k, NR^{k}C(=NR^k)NR^{k}R^k, S(O)R^k, S(O)NR^{k}R^k, S(O)$_2$R^k, NR^{k}S(O)$_2$R^k, NR^{k}S(O)$_2$NR^{k}R^k, and S(O)$_2$NR^{k}R^k; 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;

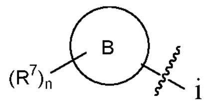
or any two R^o substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents; and

each R^e, R^i, R^k, R^o or R^p is independently selected from H, C$_{1-4}$ alkyl, C$_{3-6}$ cycloalkyl, C$_{6-10}$ aryl, 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_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, and C_{2-4} alkynyl of R^e, R^i, R^k, R^o or R^p 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} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^8, NR^8R^8, and C_{1-4} haloalkoxy, 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} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, phenyl, C_{3-10} cycloalkyl and 4-6 membered heterocycloalkyl and each R^8 is independently C_{1-6} alkyl;

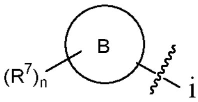
$\overset{-\,-\,-}{=\!=\!=}$ is a single bond or a double bond, wherein ring A includes at least one double bond;

the subscript n is an integer of 1, 2, 3, 4 or 5; and

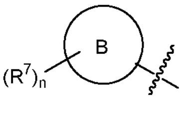
with the proviso (i) when  is 2,6-dioxohexahydropyrimidin-1-yl, 2-oxopyrrolidin-1-yl, benzo[d]thiazol-2-yl, 2-amino-4-methyl-5,6-dihydro-1,3-thiazin-4-yl, 4-methyl-6-[4-(morpholine-4-carbonyl)anilino]-5-oxo-pyrazin-2-yl, 5,7-dimethylbenzo[d]oxazol-2-yl, 6-[4-(morpholine-4-carbonyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl, 8-[4-(morpholine-4-carbonyl)anilino]imidazo[1,2-a]pyrazin-6-yl, oxazolo[4,5-b]pyridine-2-yl, or 1-methyl-2-oxo-1,6-naphthridin-3-yl, ring A in Formula (I') is not 2-pyridyl or 2-pyridyl optionally substituted with halo, methylcarboxy, 1,2,4-triazol-4-yl, 1-piperidinyl, or cyclopropyl;

(ii) when ring B is thiazolo[5,4-b]pyridin-2-yl or 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl, ring A in Formula (I') is other than 2-quinolyl;

(iii) when ring B is 1-piperazinyl, ring A in Formula (I') is not 3-(4-benzyloxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl;

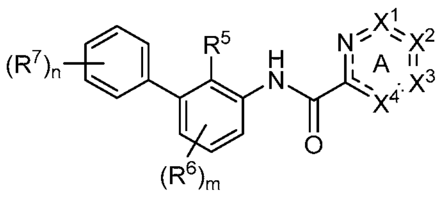
(iv) when  is 6-[1-(dimethylcarbamoyl)-3,6-dihydro-2H-pyridin-4-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl, ring A in Formula (I') is not 1-methylpyrrolo[2,3-b]pyridine-6-yl;

(v) when ring B is 2-oxo-1,2-dihydropyridin-5-yl, 2-oxo-1,2-dihydropyrazin-5-yl or 6-oxo-1H-pyridazin-3-yl, R^2 is other than t-butyl;

(vi) when  is 3,5-dimethylphenyl, R^5 is other than 4-amino-1-piperidinyl; and

(vii) the compound is other than 6-((2R,6S)-2,6-dimethylmorpholino)-N-(2-methyl-4'-(trifluoromethoxy)biphenyl-3-yl)pyridazine-3-carboxamide or N-(3-(3-acetyl-2-oxoimidazolidin-1-yl)-2-methylphenyl)-5,6,7,8-tetrahydroquinoline-2-carboxamide.

3. The compound of claim **1** or **2** 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

R^1, R^2, R^3, R^4 and R^7 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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 is C_{1-4} alkyl, halo, CN, OH, cyclopropyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, $NHOR^{11}$, $C(O)R^{11}$, $C(O)NR^{11}R^{11}$,

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}S(O)R^{11}, NR^{11}S(O)$_2$R^{11}, NR^{11}S(O)$_2$NR^{11}R^{11}, S(O)R^{11}, S(O)NR^{11}R^{11}, S(O)$_2$R^{11}, and S(O)$_2$NR^{11}R^{11}, wherein each R^{11} is independently selected from H and C$_{1-4}$ alkyl optionally substituted with 1 or 2 halo, OH, CN or OCH$_3$;

each R^6 is independently selected from H, C$_{1-4}$ alkyl, C$_{3-6}$ cycloalkyl, 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)$_2$R^{10}, NR^{10}S(O)$_2$NR^{10}R^{10}, S(O)R^{10}, S(O)NR^{10}R^{10}, S(O)$_2$R^{10}, and S(O)$_2$NR^{10}R^{10}, wherein each R^{10} is independently H or C$_{1-4}$ alkyl optionally substituted with 1 or 2 groups independently selected from halo, OH, CN and C$_{1-4}$ alkoxy, and wherein the C$_{1-4}$ alkyl, C$_{3-4}$ cycloalkyl, C$_{2-4}$ alkenyl and C$_{2-4}$ alkynyl of R^6 are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN, C$_{1-4}$ alkyl and C$_{1-4}$ alkoxy;

or two adjacent R^7 substituents, taken together with the carbon atoms to which they are attached, form a fused phenyl ring, a fused 5- to 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C$_{5-6}$ cycloalkyl ring, wherein the fused 5- to 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- to 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C$_{3-10}$ cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^q substituents;

or R^1 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C$_{3-10}$ cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C$_{5-6}$ cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^1 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C$_{3-10}$ cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^2 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^3 and X^2 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^3 and X^4 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

or R^4 and X^3 taken together form a fused phenyl ring, a fused 4- to 10-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-10} cycloalkyl ring, wherein the fused 4- to 10-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- or 6-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^b substituents;

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, 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, $NR^eC(O)R^e$, $NR^eC(O)NR^eR^e$, $NR^eC(O)OR^e$, $C(=NR^e)NR^eR^e$, $NR^eC(=NR^e)NR^eR^e$, $S(O)R^e$, $S(O)NR^eR^e$, $S(O)_2R^e$, $NR^eS(O)_2R^e$, $NR^eS(O)_2NR^eR^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-4} alkyl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl of R^d are each further optionally substituted with 1-3 independently selected R^q substituents;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, 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_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} 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^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 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, and S(O)$_2$NR^{g}R^g; wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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, 3, 4, or 5 R^n substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, R^o, NHOR^o, OR^o, SR^o, C(O)R^o, C(O)NR^{o}R^o, C(O)OR^o, OC(O)R^o, OC(O)NR^{o}R^o, NHR^o, NR^{o}R^o, NR^{o}C(O)R^o, NR^{o}C(O)NR^{o}R^o, NR^{o}C(O)OR^o, C(=NR^o)NR^{o}R^o, NR^{o}C(=NR^o)NR^{o}R^o, S(O)R^o, S(O)NR^{o}R^o, S(O)$_2$R^o, NR^{o}S(O)$_2$R^o, NR^{o}S(O)$_2$NR^{o}R^o, and S(O)$_2$NR^{o}R^o;

each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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 independently selected R^p 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_{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_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^i, SR^i, NHOR^i, C(O)R^i, C(O)NR^{i}R^i, C(O)OR^i, OC(O)R^i, OC(O)NR^{i}R^i, NHR^i, NR^{i}R^i, NR^{i}C(O)R^i, NR^{i}C(O)NR^{i}R^i, NR^{i}C(O)OR^i, C(=NR^i)NR^{i}R^i, NR^{i}C(=NR^i)NR^{i}R^i, S(O)R^i, S(O)NR^{i}R^i, S(O)$_2$R^i, NR^{i}S(O)$_2$R^i, NR^{i}S(O)$_2$NR^{i}R^i, and S(O)$_2$NR^{i}R^i, wherein the C_{1-6} alkyl, 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-, and (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each further optionally substituted by 1, 2, or 3 R^j substituents independently selected from C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, NHOR^k, OR^k, SR^k, C(O)R^k, C(O)NR^{k}R^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 $S(O)_2NR^kR^k$; 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; and

each R^e, R^i, R^k, R^o or R^p is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 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_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, and C_{2-4} alkynyl of R^e, R^i, R^k, R^o or R^p 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_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, NHR^8, NR^8R^8, and C_{1-4} haloalkoxy, wherein the C_{1-4} alkyl, phenyl and 5-6 membered heteroaryl of R^q are each optionally substituted with OH, CN, -COOH, NH_2, C_{1-4} alkoxy, C_{3-10} cycloalkyl and 4-, 5-, or 6-membered heterocycloalkyl and each R^8 is independently C_{1-6} alkyl;

the subscript n is an integer of 1, 2, 3, 4 or 5;

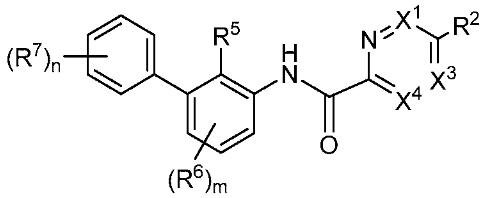
the subscript m is an integer of 1, 2 or 3; and

⎓ is a single bond or a double bond, wherein ring A includes at least one double bond;

with the proviso that the compound is other than 6-((2R,6S)-2,6-dimethylmorpholino)-N-(2-methyl-4'-(trifluoromethoxy)biphenyl-3-yl)pyridazine-3-carboxamide.

4. The compound of any one of claims **1-3**, wherein ring A is aromatic.

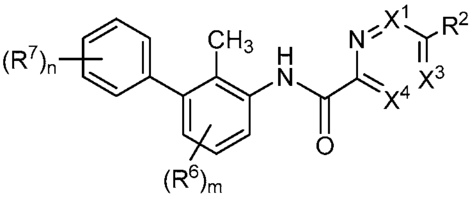
5. The compound of any one of claims **1-4**, having Formula (II):



(II)

wherein R^2 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^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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^2 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof.

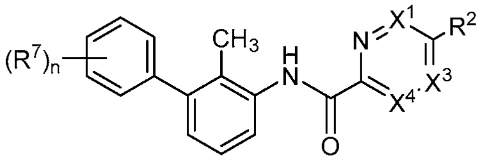
6. The compound of any one of claims **1-5**, having Formula (III):



(III)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

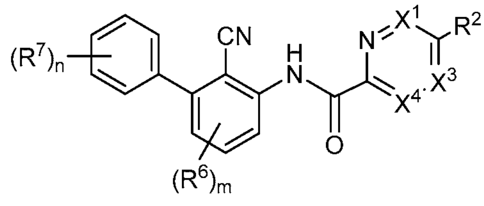
7. The compound of any one of claims **1-6**, having Formula (IV):



(IV)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

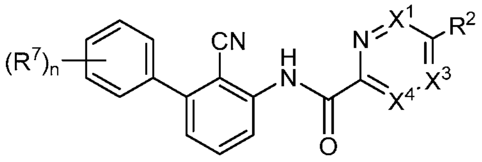
8. The compound of any one of claims **1-5**, having Formula (V):



(V)

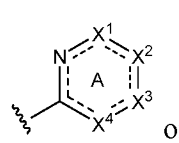
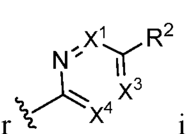
or a pharmaceutically acceptable salt or a stereoisomer thereof.

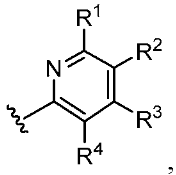
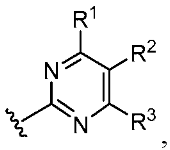
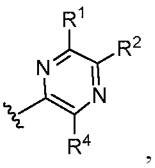
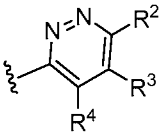
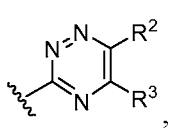
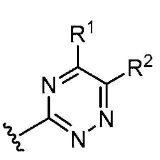
9. The compound of any one of claims **1-5** and **8**, having Formula (VI):

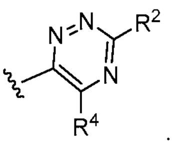


(VI)

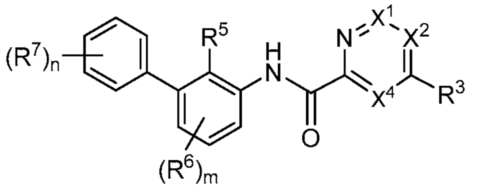
or a pharmaceutically acceptable salt or a stereoisomer thereof.

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

, , , , ,  and

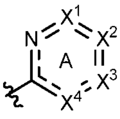
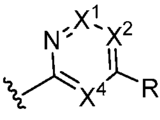
.

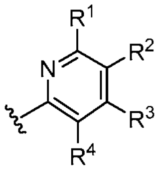
11. The compound of any one of claims **1-4**, having Formula (VII):

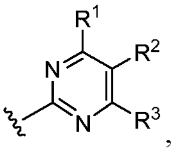


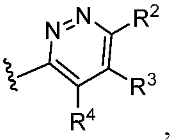
(VII)

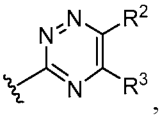
wherein R^3 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, NO_2, OR^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, $NR^aC(O)R^a$, $NR^aC(O)OR^a$, $NR^aC(O)NR^aR^a$, $C(=NR^a)R^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $NR^aS(O)R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^a$, $S(O)R^a$, $S(O)NR^aR^a$, $S(O)_2R^a$, 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^1 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof.

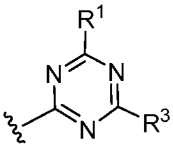
12. The compound of any one of claims **1-4** and **11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the moiety  or  is selected from:

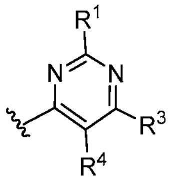


, 

, 

, 

, 

, 

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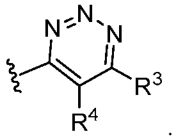
and 

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13. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is CR^1, X^3 is CR^3 and X^4 is CR^4.

14. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is CR^1, X^3 is N and X^4 is CR^4.

15. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N, X^3 is CR^3 and X^4 is CR^4.

16. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is CR^1, X^3 is CR^3 and X^4 is N.

17. The compound of any one of claims **1-10** and **13-16**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^1, R^3 and R^4, when applicable, are each independently selected from H, C_{1-6} alkyl and halo.

18. The compound of claim **11** or **12**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^1, R^2 and R^4, when applicable, are each independently selected from H, C_{1-6} alkyl and halo.

19. The compound of any one of claims **1-10** and **13-17**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is $–CH_2-R^b$.

20. The compound of claim **19**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^b is $–NR^cR^c$.

21. The compound of any of claims **11**, **12** and **18**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^3 is $–CH_2-R^b$.

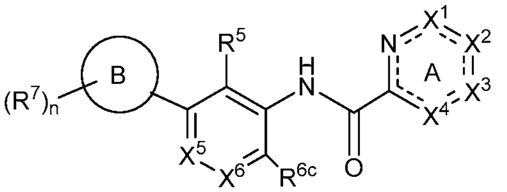
22. The compound of claim **21**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^b is $–NR^cR^c$.

23. The compound of any of claims **1-10**, and **13-16** or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is 2-hydroxyethylaminomethyl, 2-

carboxypiperidin-1-ylmethyl, (S)-2-carboxypiperidin-1-ylmethyl, (R)-2-carboxypiperidin-1-ylmethyl or (3-cyanobenzyl)oxy.

24. The compound of any of claims **1**, **2**, **11**, and **12**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^3 is 2-hydroxyethylaminomethyl, 2-carboxypiperidin-1-ylmethyl, (S)-2-carboxypiperidin-1-ylmethyl, (R)-2-carboxypiperidin-1-ylmethyl or (3-cyanobenzyl)oxy.

25. 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is CR^{6b};

ring B is phenyl, cyclohexyl, piperidinyl, or tetrahydropyridinyl;

R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, 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, OR^a, NHR^a, and NR^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^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents;

R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or CN, 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^5 are each optionally substituted with 1, 2 or 3 R^b substituents;

R^{6a}, R^{6b} and R^{6c} 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, NH_2, -NH-C_{1-4} alkyl, and -N(C_{1-4} alkyl)$_2$, wherein the C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl of R^{6a}, R^{6b}, and R^{6c} are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN, C_{1-4} alkyl and C_{1-4} alkoxy;

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

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, CN, NH_2, 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, and $NR^eC(O)R^e$, and $S(O)_2NR^eR^e$, wherein the C_{1-4} alkyl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl of R^d are each further optionally substituted with 1-3 independently selected R^f substituents;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, 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_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^b 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_{1-4} 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^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 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, and $NR^gC(O)R^g$;

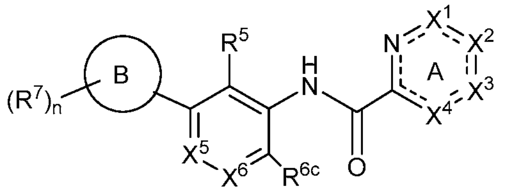
each R^g is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

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

$\overset{\cdots}{=}$ is a single bond or a double bond, wherein ring A includes at least one double bond; and

the subscript n is an integer of 1, 2, 3, 4 or 5.

26. 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is CR^{6b};

ring B is phenyl, cyclohexyl, piperidinyl, or tetrahydropyridinyl;

R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OR^a, NHR^a, and NR^aR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-

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

R^5 is C_{1-6} alkyl or CN;

R^{6a}, R^{6b} and R^{6c} 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)$_2$;

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

each R^a is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} 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^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, and NH_2;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, OH, NH_2, C(O)OR^c, NHR^c, and NR^cR^c;

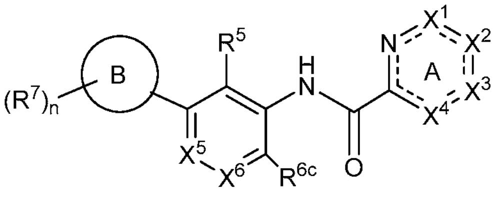
each R^c is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents independently selected from C_{1-4} alkyl, C_{1-4}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

$\overset{---}{---}$ is a single bond or a double bond, wherein ring A includes at least one double bond; and

the subscript n is an integer of 1, 2, 3, 4 or 5.

27. 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 N or CR^4;

wherein no more than two of X^1, X^2, X^3 and X^4 are simultaneously N;

X^5 is N or CR^{6a};

X^6 is CR^{6b};

ring B is phenyl, cyclohexyl, piperidinyl, or tetrahydropyridinyl;

R^1, R^2, R^3, R^4 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, OR^a, NHR^a, and NR^aR^a, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^3, R^4 and R^7 are each optionally substituted with 1 or 2, R^b substituents;

R^5 is C_{1-6} alkyl or CN;

R^{6a}, R^{6b} and R^{6c} are each independently selected from H, C_{1-4} alkyl and halo;

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

each R^a is independently selected from H, CN, 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-, 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^a are each optionally substituted with 1 or 2 R^d substituents;

each R^d is independently selected from C_{1-4} alkyl, halo, CN, and NH_2;

each R^b substituent is independently selected from halo, C_{1-4} alkyl, CN, OH, NH_2, $C(O)OR^c$, NHR^c, and NR^cR^c;

each R^c is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^c are each optionally substituted with 1, 2 or R^f substituents independently selected from C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, and OR^g;

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

$\overline{---}$ is a single bond or a double bond, wherein ring A includes at least one double bond; and

the subscript n is an integer of 1, 2, 3, 4 or 5.

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

(2S)-1-[(6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid;

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

(2S)-1-[(5-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid;

5-{[(2-hydroxyethyl)amino]methyl}-3-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

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

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide;

(2S)-1-[(6-{[(2-cyanobiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid;

N-(2-cyanobiphenyl-3-yl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide;

(2S)-1-{[6-({[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]amino}carbonyl)pyridin-3-yl]methyl}piperidine-2-carboxylic acid;

N-(2-cyano-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-5-((2-hydroxyethylamino)methyl)picolinamide;

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide;

6-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide;

(2S)-1-[(2-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid;

5-{[(2-hydroxyethyl)amino]methyl}-6-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

(2S)-1-[(5-chloro-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid;

3-chloro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

3-fluoro-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

4-[(3-cyanobenzyl)oxy]-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4-(pyridin-3-ylmethoxy)pyridine-2-carboxamide;

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4-(pyridin-2-ylmethoxy)pyridine-2-carboxamide;

3-(dimethylamino)-5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

(2S)-1-[(2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-4-yl)methyl]piperidine-2-carboxylic acid;

4-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

N-(2-methylbiphenyl-3-yl)-6-(pyridin-3-ylmethoxy)pyrimidine-4-carboxamide;

4-cyano-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

N-(2-methylbiphenyl-3-yl)pyrazine-2-carboxamide;

N-(2-methylbiphenyl-3-yl)pyrimidine-4-carboxamide;

N-(2-methylbiphenyl-3-yl)pyrimidine-2-carboxamide;

N-(2-methylbiphenyl-3-yl)pyridazine-3-carboxamide; and

N-(2-methylbiphenyl-3-yl)-2-(pyridin-3-ylmethoxy)pyrimidine-4-carboxamide; or a pharmaceutically acceptable salt or a stereoisomer thereof.

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

5-{[(2-hydroxyethyl)amino]methyl}-N-(2-methylbiphenyl-3-yl)-4,4'-bipyridine-2-carboxamide;

(2S)-1-[(4-methyl-6-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-3-yl)methyl]piperidine-2-carboxylic acid;

5-{[(2-hydroxyethyl)amino]methyl}-4-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

4-(cyclopropylmethoxy)-5-((2-hydroxyethylamino)methyl)-N-(2-methylbiphenyl-3-yl)picolinamide;

5-{[(2-hydroxyethyl)amino]methyl}-4-methoxy-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

(2S)-1-[(5-methyl-2-{[(2-methylbiphenyl-3-yl)amino]carbonyl}pyridin-4-yl)methyl]piperidine-2-carboxylic acid;

4-{[(2-hydroxyethyl)amino]methyl}-5-methyl-N-(2-methylbiphenyl-3-yl)pyridine-2-carboxamide;

N-(2-cyano-3-cyclohex-1-en-1-ylphenyl)-5-{[(2-hydroxyethyl)amino]methyl} pyridine-2-carboxamide;

N-(2-cyano-3-piperidin-1-ylphenyl)-5-{[(2-hydroxyethyl)amino]methyl} pyridine-2-carboxamide;

tert-butyl 5-(2-cyano-3-{[(5-{[(2-hydroxyethyl)amino]methyl}pyridin-2-yl)carbonyl]amino}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate;

N-(2-cyano-3-cyclohexylphenyl)-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide;

(S)-1-((6-(3-methyl-2-phenylpyridin-4-ylcarbamoyl)pyridin-3-yl)methyl)piperidine-2-carboxylic acid;

5-{[(2-hydroxyethyl)amino]methyl}-N-(3-methyl-2-phenylpyridin-4-yl)pyridine-2-carboxamide;

N-[2-cyano-3-(3,4-dihydro-2H-pyran-5-yl)phenyl]-5-{[(2-hydroxyethyl)amino] methyl}pyridine-2-carboxamide;

N-[3-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-fluoro-2-methylphenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide;

N-[2-cyano-3-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide;

N-[2-cyano-3-(2,3-dihydro-1-benzofuran-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide;

N-[2-cyano-3-(2-methyl-2H-indazol-6-yl)phenyl]-5-{[(2-hydroxyethyl)amino]methyl}pyridine-2-carboxamide; and

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

or a pharmaceutically acceptable salt or a stereoisomer thereof.

30. A pharmaceutical composition comprising a compound of any one of claims **1-29**, or a pharmaceutically acceptable salt or a stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.

31. A method of inhibiting PD-1/PD-L1 interaction, said method comprising administering to a patient a compound of any one of claims **1-29** or a pharmaceutically acceptable salt or a stereoisomer thereof.

32. A method of treating a disease or disorder associated with 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 **1-29**, or a pharmaceutically acceptable salt or a stereoisomer thereof, or a composition of claim **30**.

33. The method of claim **32**, wherein the disease or disorder is a viral infection or cancer.

34. A method of enhancing, stimulating, modulating 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 of claims **1-29,** or a pharmaceuticallyacceptable salt thereof or a stereoisomer thereof, or a composition of claim **30**.

35. A method of inhibiting growth, proliferation, or metastasis of cancer cells in a patient, said method comprising administering to the patient in need thereof a therapeutically effective amount of a compound of any of claims **1-29,** or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, or a composition of claim **30**.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/81 C07D401/06 A61K31/44 A61K31/4545 A61P31/00
A61P35/00 A61P37/04 C07D213/84 C07D237/24 C07D239/28
C07D241/24 C07D401/12 C07D401/14 C07D405/12 C07D405/14

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, CHEM ABS Data, 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	WO 2015/101622 A1 (BAYER CROPSCIENCE AG [DE]) 9 July 2015 (2015-07-09) claims 1, 9 -----	1,2,4, 10,12-24
X	WO 2014/138484 A1 (AMGEN INC [US]) 12 September 2014 (2014-09-12) claims 1, 12, 52 -----	1,2,4, 10, 12-22,30
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☒ Further documents are listed in the continuation of Box C.

☒ 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

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"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

28 March 2017

Date of mailing of the international search report

24/04/2017

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2013/157021 A1 (ADVINUS THERAPEUTICS LTD [IN]) 24 October 2013 (2013-10-24) claims 1, 10 page 39, line 20 - page 40, line 8 page 32, formula (III); and page 47, compound "INT-2-XI" -----	1,2,4, 10, 12-24, 30,32, 33,35
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X	EP 2 233 474 A1 (EISAI R&D MAN CO LTD [JP]) 29 September 2010 (2010-09-29) claims 1, 9, 11 -----	1,2,4, 10, 12-19, 21,30
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X	WO 2006/053121 A2 (CGI PHARMACEUTICALS INC [US]; CURRIE KEVIN S [US]; KROPF JEFFREY E [US) 18 May 2006 (2006-05-18) claims 1, 22, 42-44, 50, 62, 90 -----	1,2,4, 10, 12-24, 30,32, 33,35
X	WO 2005/034869 A2 (IRM LLC [US]; DING QIANG [US]; XIE YONGPING [US]; GRAY NATHANAEL SCHIA) 21 April 2005 (2005-04-21) claims 1, 4, 5 page 6, paragraph [0019] - page 12, paragraph [0040] -----	1,2,4, 10, 12-22, 30,32, 33,35

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E	WO 2017/035405 A1 (ACHILLION PHARMACEUTICALS INC [US]) 2 March 2017 (2017-03-02) page 145; "Structure 3" the last fomula on page 158	1-3,13, 18,25-27
X	WO 2011/082400 A2 (HARVARD COLLEGE [US]; SHARPE ARLENE H [US]; BUTTE MANISH J [US]; OYAMA) 7 July 2011 (2011-07-07) the whole document; in particular, claims 1, 3, 10, and 78	1-19,21, 25-27, 30-35
A	WO 2015/034820 A1 (SQUIBB BRISTOL MYERS CO [US]) 12 March 2015 (2015-03-12) the whole document	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/067155

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