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(54) **HETEROCYCLIC COMPOUNDS AS IMMUNOMODULATORS**

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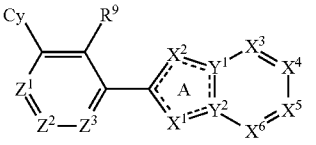
(57) **ABSTRACT**

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.

(I')



HETEROCYCLIC COMPOUNDS AS IMMUNOMODULATORS

FIELD OF THE INVENTION

[0001] 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

[0002] 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.

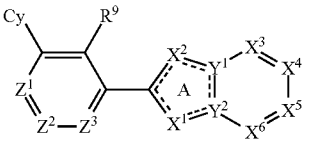
[0003] Programmed cell death-1 (PD-1), also known as CD279, is a cell surface receptor expressed on activated T cells, natural killer T cells, B cells, and macrophages (Greenwald et al, Annu. Rev. Immunol 2005, 23:515-548; Okazaki and Honjo, Trends Immunol 2006, (4):195-201). It functions as an intrinsic 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).

[0004] 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, PNAS 2002, 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).

[0005] 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

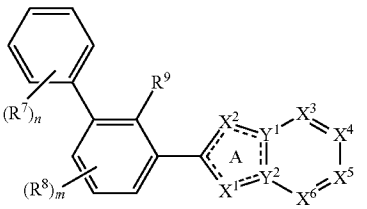
[0006] The present disclosure provides, inter alia, a compound of Formula (I'):



(I')

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

[0007] The present disclosure further provides a compound of Formula (I):



(I)

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

[0008] 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.

[0009] The present disclosure further provides methods of modulating or inhibiting PD-1/PD-L1 protein/protein inter-

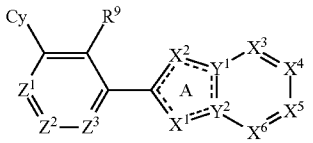
action, which comprises administering to an individual a compound of the disclosure, or a pharmaceutically acceptable salt or a stereoisomer thereof.

[0010] 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

[0011] The present disclosure provides, inter alia, a compound of Formula (I'):



(I')

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

[0012] one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;

[0013] X^1 is N or CR^1;

[0014] X^2 is N or CR^2;

[0015] X^3 is N or CR^3;

[0016] X^4 is N or CR^4;

[0017] X^5 is N or CR^5;

[0018] X^6 is N or CR^6;

[0019] Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents;

[0020] Z^1 is N or CR^{8a};

[0021] Z^2 is N or CR^{8b};

[0022] Z^3 is N or CR^{8c};

[0023] R^1, R^2, R^{8a}, R^{8b} and R^{8c} are each independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, $—NHR^{10}$, $—NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^{8a}, R^{8b}, R^{8c} and R^{10} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

[0024] R^9 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^9 are each optionally substituted with 1, 2 or 3 R^b substituents;

[0025] each R^{11} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^{11} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

[0026] R^3, R^4, R^5, R^6 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^3, R^4, R^5, R^6 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, with the proviso that at least one of R^3, R^4, R^5 and R^6 is other than H;

[0027] or two adjacent R^7 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocy-

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

[0028] 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;

[0029] 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^h substituents;

[0030] each R^h 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;

[0031] 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, $NHOR^o$, 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 $S(O)_2NR^oR^o$;

[0032] 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 hetero cycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^g are each optionally substituted with 1-3 R^p substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR^rR^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR^rR^r$, NHR^r, NR^rR^r, $NR^rC(O)R^r$, $NR^rC(O)NR^rR^r$, $NR^rC(O)OR^r$, $C(=NR^r)NR^rR^r$, $NR^rC(=NR^r)NR^rR^r$, $NR^cC(=NOH)NR^rR^r$, $NR^rC(=NCN)NR^rR^r$, $S(O)R^r$, $S(O)NR^rR^r$, $S(O)_2R^r$, $NR^rS(O)_2R^r$, $NR^rS(O)_2NR^rR^r$ and $S(O)_2NR^rR^r$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

[0033] 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_{2-6} alkenyl, C_{2-6} alkynyl, 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- 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, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} 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;

[0034] 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;

[0035] 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;

[0036] 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;

[0037] 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;

[0038] 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;

[0039] 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

[0040] 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, 4-7 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, 4-7 membered heterocycloalkyl, 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;

[0041] 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^{12}, $NR^{12}R^{12}$, 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^{12} is independently C_{1-6} alkyl;

[0042] ----- is a single bond or a double bond to maintain ring A being aromatic; and

[0043] with the proviso that the compound is other than 6-(6-chloro-3-methylimidazol[1,2-a]pyridine-2-yl)-4-(4-chlorophenyl)-(1,1-dimethylethoxy)-2,5-dimethyl-3-pyridineacetic acid or 6-(6-chloroimidazol[1,2-a]pyridine-2-yl)-4-(4-chlorophenyl)-(1,1-dimethylethoxy)-2,5-dimethyl-3-pyridineacetic acid, or enantiomers thereof.

[0044] The present disclosure provides a compound of Formula (I'), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

[0045] one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;

[0046] X^1 is N or CR^1;

[0047] X^2 is N or CR^2;

[0048] X^3 is N or CR^3;

[0049] X^4 is N or CR^4;

[0050] X^5 is N or CR^5;

[0051] X^6 is N or CR^6;

[0052] Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents;

[0053] Z^1 is N or CR^{8a};

[0054] Z^2 is N or CR^{8b};

[0055] Z^3 is N or CR^{8c};

[0056] R^1, R^2, R^{8a}, R^{8b} and R^{8c} are each independently selected from H, C_{1-4} alkyl, C_{3-4} 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 selected from H and 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^1, R^2, R^{8a}, R^{8b}, or R^{8c} are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN and C_{1-4} alkoxy;

[0057] R^9 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 C_{1-4} alkyl, cyclopropyl, C_{2-4} alkynyl and C_{1-4} alkoxy of R^9 are each optionally substituted with 1 or 2 substituents selected from halo, OH, CN and OCH_3 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 substituents;

[0058] R^3, R^4, R^5, R^6 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^3, R^4, R^5, R^6 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, with the proviso that at least one of R^3, R^4, R^5 and R^6 is other than H;

[0059] or two adjacent R^7 substituents on the Cy ring, taken together with the atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{3-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{3-6} cycloalkyl ring are each optionally substituted with 1, 2 or 3 independently selected R^b substituents or 1, 2 or 3 independently selected R^q substituents;

[0060] 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;

[0061] 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;

[0062] 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, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^i)NR^cR^c$, $NR^cC(=NR^i)NR^cR^c$, 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;

[0063] 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 hetero cycloalkyl, 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, $NHOR^o$, 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 $S(O)_2NR^oR^o$;

[0064] 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;

[0065] or any two R^q 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-, (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;

[0066] 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;

[0067] 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;

[0068] 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;

[0069] 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;

[0070] 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;

[0071] 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

[0072] 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;

[0073] each R^q is independently selected from OH, CN, —COOH, NH_2, halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12}, $NR^{12}R^{12}$, 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^{12} is independently C_{1-6} alkyl; and

[0074] ⋯ is a single bond or a double bond to maintain ring A being aromatic.

[0075] In some embodiments of compounds of Formula (I'), Cy is C_{6-10} aryl, optionally substituted with 1 to 4 independently selected R^7 substituents. In certain embodiments, Cy is phenyl or naphthyl, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents. In certain embodiments, Cy is phenyl optionally substituted with 1 to 4 independently selected R^7 substituents. In certain embodiments, Cy is unsubstituted phenyl.

[0076] In some embodiments of compounds of Formula (I'), Cy is C_{3-10} cycloalkyl, optionally substituted with 1 to 4 independently selected R^7 substituents. In certain embodiments, Cy is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl or cyclooctyl, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents.

[0077] In some embodiments of compounds of Formula (I'), Cy is 5- to 14-membered heteroaryl, optionally substituted with 1 to 4 independently selected R^7 substituents. In certain embodiments, Cy 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, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents.

[0078] In some embodiments of compounds of Formula (I'), Cy is 4- to 10-membered heterocycloalkyl, optionally substituted with 1 to 4 independently selected R^7 substituents. In certain embodiments, Cy 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, and thiomorpholino, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents. In some embodiments, Cy is 3-dihydro-1,4-benzodioxin-6-yl optionally substituted with 1 to 4 independently selected R^7 substituents.

[0079] In some embodiments of compounds of Formula (I'), Z^1 is CR^{8a}, Z^2 is CR^{8b} and Z^3 is CR^{8c}. In certain instances, R^{8a}, R^{8b} and R^{8c} are each H.

[0080] In some embodiments of compounds of Formula (I'), Z^1 is CR^{8a}, Z^2 is N and Z^3 is N. In certain instances, R^{8a} is H.

[0081] In some embodiments of compounds of Formula (I'), Z^1 is CR^{8a}, Z^2 is N and Z^3 is CR^{8c}. In certain instances, R^{8a} and R^{8c} are each H.

[0082] In some embodiments of compounds of Formula (I'), Z^1 is CR^{8a}, Z^2 is CR^{8b} and Z^3 is N. In certain instances, R^{8a} and R^{8b} are each H.

[0083] In some embodiments of compounds of Formula (I'), Z^1 is N, Z^2 is CR^{8b} and Z^3 is CR^{8c}. In certain instances, R^{8b} and R^{8c} are each H.

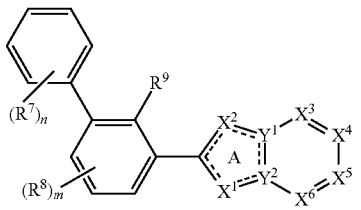
[0084] In some embodiments of compounds of Formula (I'), Z^1 is N, Z^2 is N and Z^3 is CR^{8c}. In certain instances, R^{8c} is H.

[0085] In some embodiments of compounds of Formula (I'), Z^1 is N, Z^2 is CR^{8b} and Z^3 is N. In certain instances, R^{8b} is H.

[0086] In some embodiments of compounds of Formula (I'), Z^1, Z^2 and Z^3 are each N.

[0087] In some embodiments, the present disclosure provides compounds of Formula (I):

(I)



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

[0088] one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;

[0089] X^1 is N or CR^1;

[0090] X^2 is N or CR^2;

[0091] X^3 is N or CR^3;

[0092] X^4 is N or CR^4;

[0093] X^5 is N or CR^5;

[0094] X^6 is N or CR^6;

[0095] R^1, R^2 and R^8 are each independently selected from H, C_{1-4} alkyl, C_{3-4} 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 the C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{2-4} alkenyl and C_{2-4} alkynyl of R^1, R^2 or R^8 are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN and C_{1-4} alkoxy;

[0096] R^9 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 H or C_{1-4} alkyl optionally substituted with 1 or 2 halo, OH, CN or OCH_3;

[0097] R^3, R^4, R^5, R^6 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^3, R^4, R^5, R^6 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, with the proviso that at least one of R^3, R^4, R^5 and R^6 is other than H;

[0098] or two adjacent R^7 substituents on the phenyl ring, taken together with the carbon atoms to which they are attached, form a fused phenyl ring, a fused 5- or 6-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{5-6} cycloalkyl ring, wherein the fused 5- or 6-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^q substituents;

[0099] 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;

[0100] 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;

[0101] 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, $NR^cC(O)R^c$, $NR^cC(O)OR^c$, $NR^cC(O)NR^cR^c$, $NR^cS(O)R^c$, $NR^cS(O)_2R^c$, $NR^cS(O)_2NR^cR^c$, $S(O)R^c$, $S(O)NR^cR^c$, $S(O)_2R^c$ or $S(O)_2NR^cR^c$; 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;

[0102] 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 hetero cycloalkyl, 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-, and (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^{11} substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, 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;

[0103] 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;

[0104] 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-, (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 attach 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;

[0105] 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;

[0106] 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;

[0107] 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;

[0108] 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;

[0109] 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;

[0110] 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

[0111] 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;

[0112] 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^{12}, NR^{12}R^{12}, 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 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl;

[0113] ----- is a single bond or a double bond to maintain ring A being aromatic;

[0114] the subscript n is an integer of 1, 2, 3, 4 or 5; and

[0115] the subscript m is an integer of 1, 2, 3 or 4. In some embodiments, the subscript m is an integer of 1, 2 or 3.

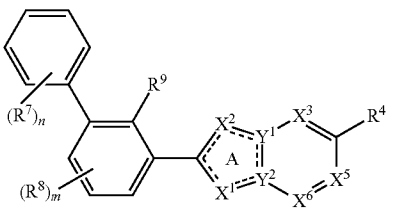
[0116] In some embodiments, R^9 is C_{1-4} alkyl, halo, CN, OH, cyclopropyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, —NH—C_{1-4} alkyl, —N(C_{1-4} alkyl)$_2$, NHOR^{11}, C(O)R^{11}, C(O)NR^{11}R^{11}, C(O)OR^{11}, OC(O)R^{11}, OC(O)NR^{11}R^{11}, NR^{11}C(O)R^{11}, 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 C_{1-4} alkyl, cyclopropyl, C_{2-4} alkynyl and C_{1-4} alkoxy of R^9 are each optionally substituted with 1 or 2 substituents selected from halo, OH, CN and OCH_3 and each R^{11} is independently H or C_{1-4} alkyl optionally substituted with 1 or 2 halo, OH, CN or OCH_3.

[0117] 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 fused phenyl ring, a fused 5- or 6-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{5-6} cycloalkyl ring, wherein the fused 5- or 6-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 1 or 2 independently selected R^q substituents. 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.

[0118] In some embodiments, the present disclosure provides compounds having Formula (II):

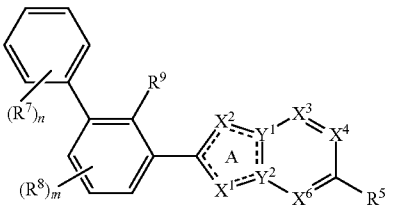
(II)



or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^4 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. Other variables of Formula (II) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein. In one embodiment of compounds of Formula (II), R^9 is CN or C_{1-4} alkyl optionally substituted with R^q. In another embodiment, R^9 is CH_3 or CN.

[0119] In some embodiments, the present disclosure provides compounds having Formula (IIa):

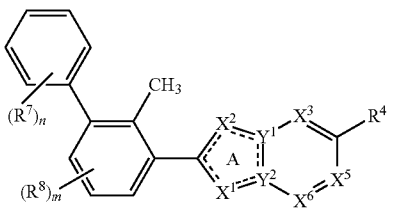
(IIa)



or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein 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^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. Other variables of Formula (IIa) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I) as described herein. In one embodiment of compounds of Formula (II), R^9 is CN or C_{1-4} alkyl optionally substituted with R^q. In another embodiment, R^9 is CH_3 or CN.

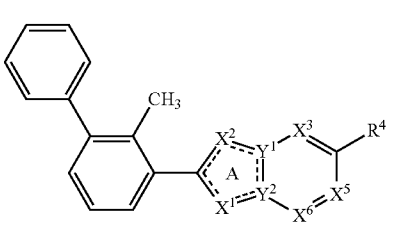
[0120] In some embodiments, the present disclosure provides compounds having Formula (III):

(III)



or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (III) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein.

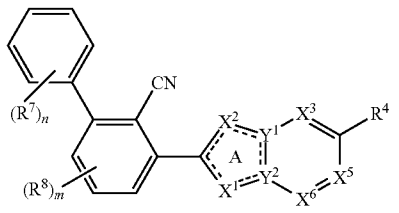
[0121] In some embodiments, the present disclosure provides compounds having Formula (IV):



(IV)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (IV) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein.

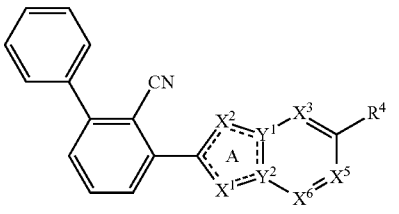
[0122] In some embodiments, the present disclosure provides compounds having Formula (V):



(V)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (V) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein.

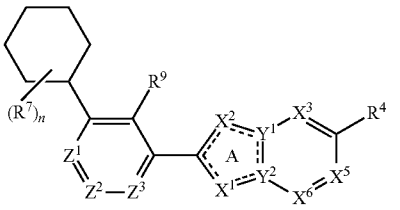
[0123] In some embodiments, the present disclosure provides compounds having Formula (VI):



(VI)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (VI) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein.

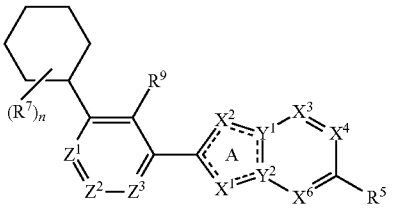
[0124] In some embodiments, the present disclosure provides compounds having Formula (VII):



(VII)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (VII) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein. In some instances, R^7 is H, n is 1, Z^1 is CR^{8a}, Z^2 is CR^{8b} and Z^3 is CR^{8c}. In certain instances, Z^1, Z^2 and Z^3 are each H.

[0125] In some embodiments, the present disclosure provides compounds having Formula (VIII):

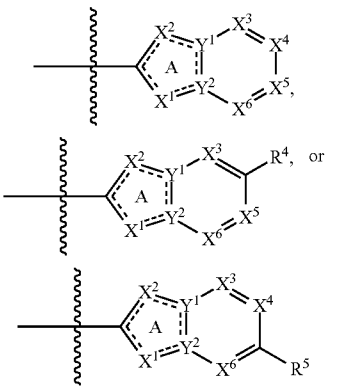


(VIII)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the variables of Formula (VIII) are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein. In some instances, R^7 is H, n is 1, Z^1 is CR^{8a}, Z^2 is CR^{8b} and Z^3 is CR^{8c}. In certain instances, Z^1, Z^2 and Z^3 are each H.

[0126] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or

[0127] VIII, or a pharmaceutically acceptable salt or a stereoisomer thereof, the moiety:



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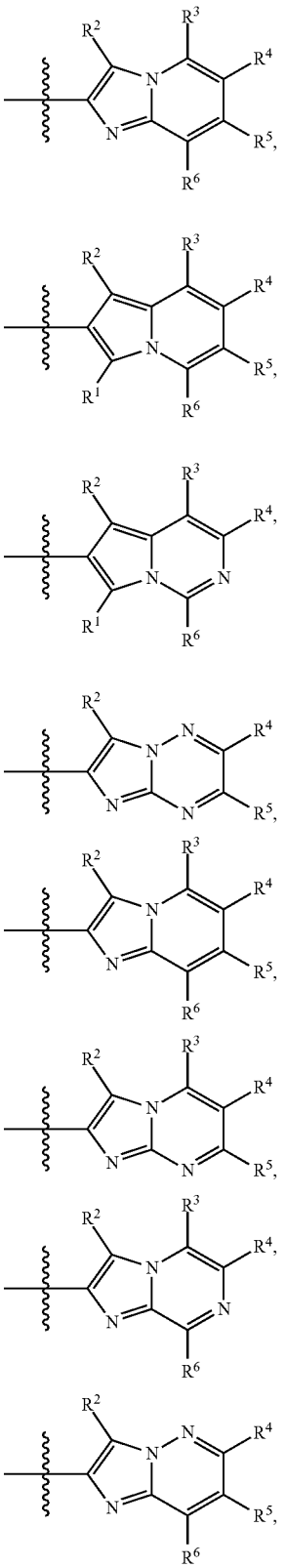

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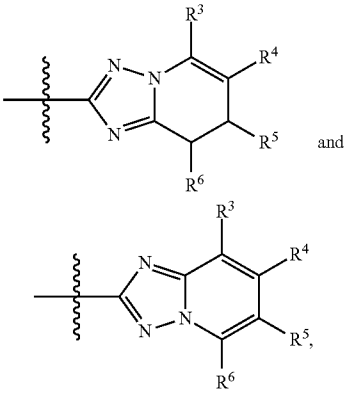
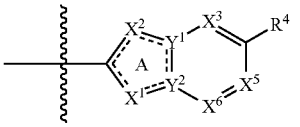


and

wherein the substituents R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein. In certain embodiments, at each occurrence, R^1, R^2, R^3 and R^5 are each H.

[0128] In some embodiments, the moiety:



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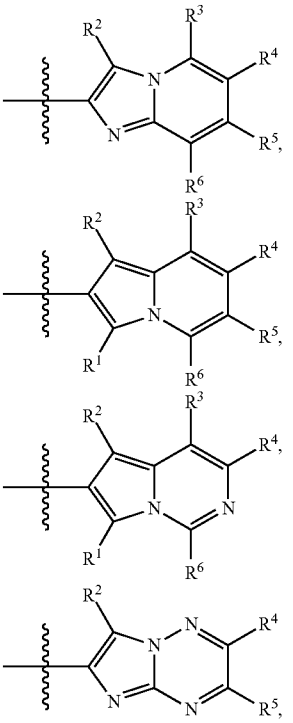

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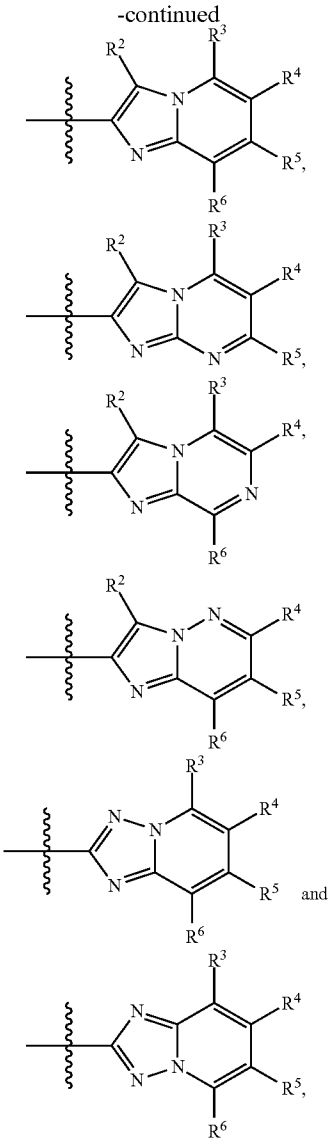


wherein the substituents R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in Formula (I') or (I) or any embodiment of compounds of Formula (I') or (I) as described herein. In certain embodiments, at each occurrence, R^1, R^2, R^3 and R^5 are each H.

[0129] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1 is N, X^2 is CH, X^3, X^5 and X^6 are each CH, Y^1 is N and Y^2 is C.

[0130] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1 is CH, X^2 is CH, X^3, X^5 and X^6 are each CH, Y^1 is C and Y^2 is N.

[0131] In some embodiments of compounds of Formula I', I, II, III, IV, V, VI, or VII, X^1 is CH, X^2 is CH, X^3 and X^6 are each CH, X^5 is N, Y^1 is C and Y^2 is N.

[0132] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1 is N, X^2 is CH, X^3 and X^6 are each N, X^5 is CH, Y^1 is N and Y^2 is C.

[0133] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1 is N, X^2 is CH, X^3 and X^5 are each CH, X^6 is N, Y^1 is N and Y^2 is C.

[0134] In some embodiments of compounds of Formula I', I, II, III, IV, V, VI, or VII, X^1 is N, X^2 is CH, X^3 and X^6 are each CH, X^5 is N, Y^1 is N and Y^2 is C.

[0135] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1 is N, X^2 is CH, X^5 and X^6 are each CH, X^3 is N, Y^1 is N and Y^2 is C.

[0136] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1 and X^2 are each N, X^3, X^5 and X^6 are each CH, Y^1 is C and Y^2 is N.

[0137] In some embodiments of compounds of Formula I', I, II, III, IV, V, VI, or VII, X^1 and X^2 are each N, X^3 is CH, X^5 is N, X^6 is CR^6, Y^1 is C and Y^2 is N.

[0138] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1 is N, X^2 is CH, X^3 and X^5 are each CH, X^6 is CR^6, Y^1 is N and Y^2 is C.

[0139] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, or VI, VII, or VIII, X^1 and X^2 are each N, X^3 and X^5 are each CH, X^6 is CR^6, Y^1 is N and Y^2 is C.

[0140] In some embodiments, R^9 is C_{1-4} alkyl or CN.

[0141] In some embodiments, R^9 is CH_3 or CN.

[0142] In some embodiments, R^7 and R^8 are each H.

[0143] In some embodiments, R^{8a}, R^{8b}, and R^{8c} are each H.

[0144] In some embodiments, R^7, R^{8a}, R^{8b}, and R^{8c} are each H.

[0145] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^2, X^3, X^5 and X^6 are each CH.

[0146] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1, X^2, X^3, X^5 and X^6 are each CH.

[0147] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^1, X^2, X^3 and X^6 are each CH.

[0148] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^2 and X^5 are each CH.

[0149] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^2, X^3 and X^5 are each CH.

[0150] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^2 and X^6 are each CH.

[0151] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^2, X^5 and X^6 are each CH.

[0152] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^3, X^5 and X^6 are each CH.

[0153] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, X^3 is CH.

[0154] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, R^4 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-carb oxypiperidin-1-yl, (cyanomethyl)amino, (S)-2-carboxypiperidin-1-yl, (R)-2-carboxypiperidin-1-yl or 2-carboxypiperidin-1-yl. In other embodiments, R^4 is C_{1-4} alkyl substituted with R^d. In other embodiments, R^4 is C_{1-4} alkyl substituted with R^f. In other embodiments, R^4 is C_{1-4} alkyl substituted with R^h. In other embodiments, R^4 is C_{1-4} alkyl substituted with R^i. In other embodiments, R^4 is C_{1-4} alkyl substituted with R^n. In other embodiments, R^4 is C_{1-4} alkyl substituted with R^q.

[0155] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, R^4 is —CH_2R^h. 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. In other embodiments, R^4 is $—CH_2—R^d$. In other embodiments, R^4 is $—CH_2—R^f$. In other embodiments, R^4 is $—CH_2—R^h$. In other embodiments, R^4 is $—CH_2—R^j$. In other embodiments, R^4 is $—CH_2—R^n$. In other embodiments, R^4 is $—CH_2—R^q$.

[0156] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, R^4 is 2-hydroxyethylaminomethyl, 2-hydroxyethyl(methyl)aminomethyl, 2-carboxypiperidin-1-ylmethyl, (cyanomethyl)aminomethyl, (S)-2-carboxypiperidin-1-ylmethyl, (R)-2-carboxypiperidin-1-ylmethyl or 2-carboxypiperidin-1-ylmethyl.

[0157] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, R^6 is H, halo or C_{1-6} alkyl optionally substituted with 1-3 R^q substituents.

[0158] In some embodiments of compounds of Formula I', I, II, IIa, III, IV, V, VI, VII, or VIII, R^6 is H, halo or CH_3.

[0159] 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 (I) can be combined in any suitable combination.

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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.

[0166] 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.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] The term "amino" refers to a group of formula —NH_2.

[0171] The term "carbamyl" refers to a group of formula —$C(O)NH_2$.

[0172] 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).

[0173] The term "cyano" or "nitrile" refers to a group of formula —C≡N, which also may be written as —CN.

[0174] 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.

[0175] The term "haloalkyl" as used herein refers to an alkyl group in which one or more of the hydrogen atoms has been replaced by a halogen atom. The term "C_{n-m} haloalkyl" refers to a C_{n-m} alkyl group having n to m carbon atoms and from at least one up to {2(n to m)+1} halogen atoms, which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5 and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

[0176] 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.

[0177] 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.

[0178] The term "sulfido" refers to a sulfur atom as a divalent substituent, forming a thiocarbonyl group (C=S) when attached to carbon.

[0179] 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).

[0180] 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.

[0181] 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.

[0182] 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.

[0183] 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.

[0184] 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.

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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.

[0191] 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., 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H-isoindole and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

[0192] 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.

[0193] 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.

[0194] 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.

[0195] 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.

[0196] 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.

[0197] 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.

[0198] 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

[0199] 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.

[0200] 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.

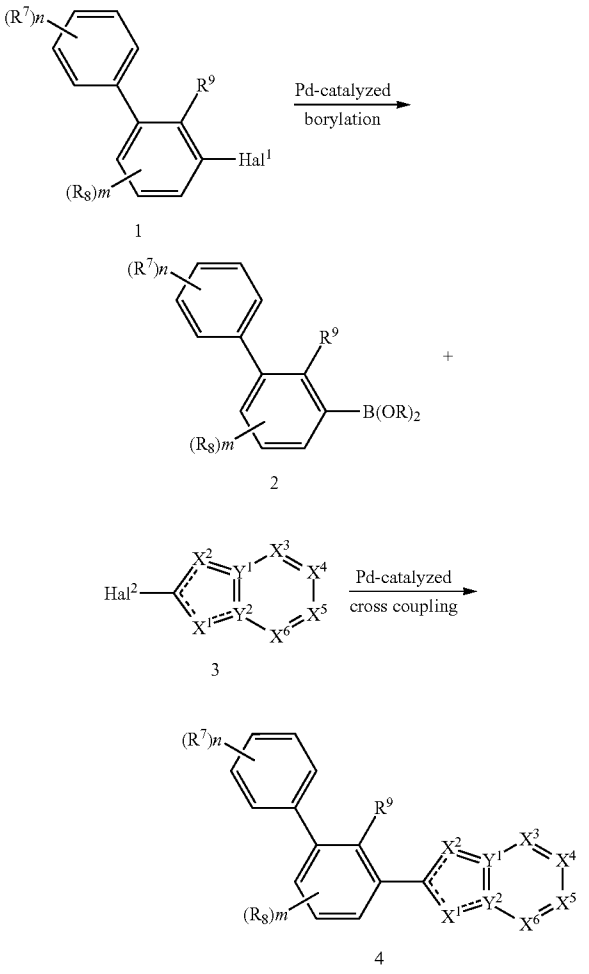
[0201] Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, e.g., in Kocienski, *Protecting Groups,* (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith et al., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 6th Ed. (Wiley, 2007); Peturssion et al., "Protecting Groups in Carbohydrate Chemistry," *J.* Chem. Educ., 1997, 74(11), 1297; and Wuts et al., *Protective Groups in Organic Synthesis,* 4th Ed., (Wiley, 2006).

[0202] 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).

[0203] 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.

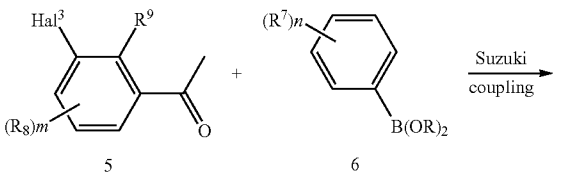
[0204] Compounds of formula (I') or (I) can be prepared, e.g., using a process as illustrated in Schemes 1-5.

Scheme 1



[0205] The compounds of Formula 4 can be prepared according to Scheme 1. The halo group (e.g., Hal^1=Cl, Br, I) of biphenyl compounds 1 can be converted to the boronic esters 2 under standard conditions [e.g., in the presence of bis(pinacolato)diboron and a palladium catalyst, such as, tetrakis(triphenylphosphine) palladium(0), palladium(II) acetate]. Boronates 2 can react with the heteroaryl halides 3 (e.g., Hal^2=Cl, Br, I) under standard Suzuki coupling condition (e.g., in the presence of a palladium catalyst and a suitable base) to give the N-bridged bicyclic compounds 4.

Scheme 2



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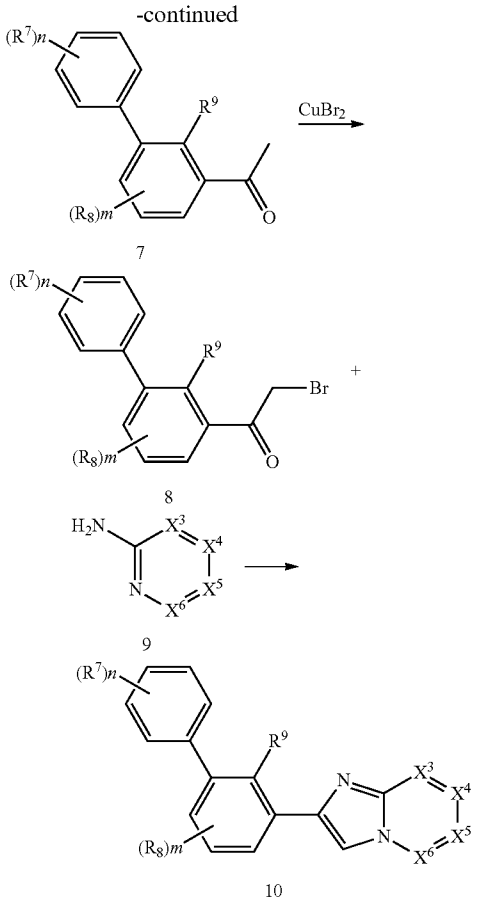
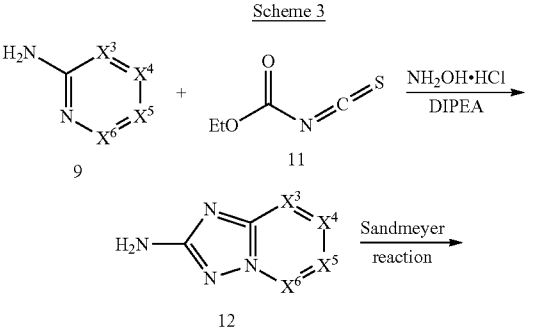


[0206] The N-bridged heteroaryl compounds of Formula 10 can also be prepared according to Scheme 2. Briefly, the halo group of the substituted phenyl ethanone 5 (e.g., Hal^3=Cl, Br or I) can be coupled with substituted phenyl boronic esters 6 under standard Suzuki coupling condition (e.g., in the presence of a palladium catalyst and a suitable base) to produce the biphenyl compounds 7. Bromination of the methyl ketones 7 using brominating reagents including, but not limited, to copper(II) bromide can generate α-bromo ketones 8. Condensation of α-bromo ketones 8 and amino heterocycles 9 in polar solvents (e.g., isopropanol) under heating can afford the N-bridged heteroaryl compounds 10.

Scheme 3



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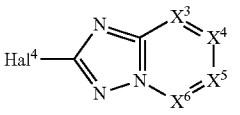

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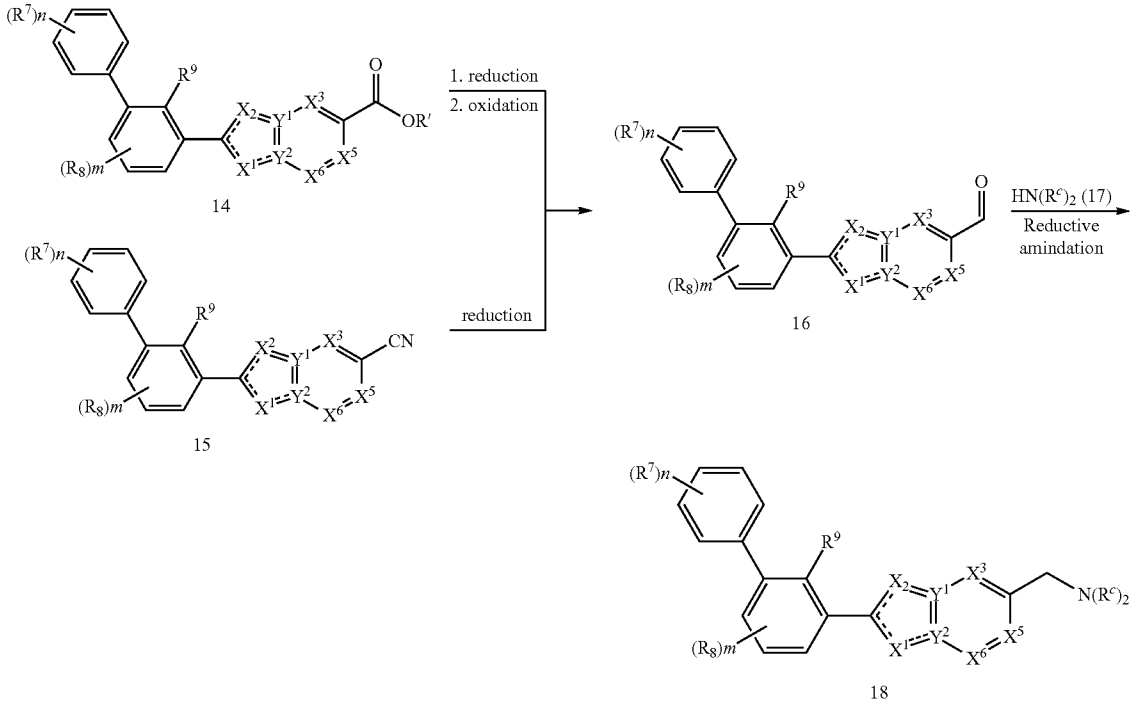
[0207] The triazole-containing heteroaryl halides of formula 13 (Hal^4 is a halide such as Br or I) can be formed according to Scheme 3. Coupling of amino heterocycles 9 with ethoxycarbonyl isothiocyanate 11, followed by treatment with hydroxylamine hydrochloride and diisopropylethylamine (DIPEA) can form N-bridged heteroaryl amines 12. Conversion of the primary amine in 12 to halides can be achieved under Sandmeyer reaction conditions [i.e. in the presence of tert-butyl nitrite and a halogen sources such as $CuBr_2$ or I_2] to generate the N-bridged heteraryl halides 13.

Scheme 4



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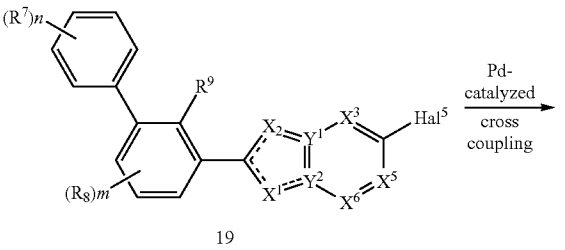
[0208] The N-bridged heteroaryl compounds of Formula 18 can be prepared according to Scheme 4, starting from compounds of formula 14 or 15 which can be prepared according to procedures as described in Scheme 1 or 2. Heteroaryl esters 14 can be reduced to aldehydes 16 via a sequence of reduction (e.g., $LiAlH_4$ or $LiBH_4$ as reducing reagents) and oxidation (e.g., Dess-Martin periodinane as oxidant). The aldehydes 16 might also be formed via direct reduction of esters 14 under mild reducing conditions [e.g., using diisobutylaluminium hydride (DIBAL) as the reducing agent at low temperature]. Alternatively, aldehydes 16 can be formed through a direct reduction of nitriles 15 with DIBAL as the reducing reagent at low temperature. Then the aldehydes 16 can react with amines 17 of formula HNR^cR^c under standard reductive amination conditions (e.g., sodium triacetoxyborohydride or sodium cyanoborohydride as reducing reagents) to generate compounds of formula 18.

Scheme 5



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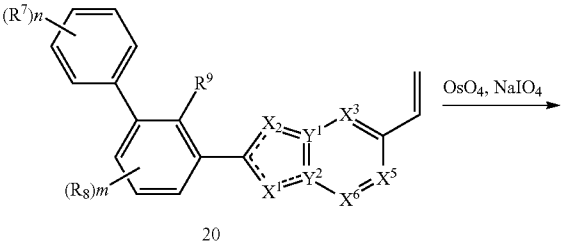

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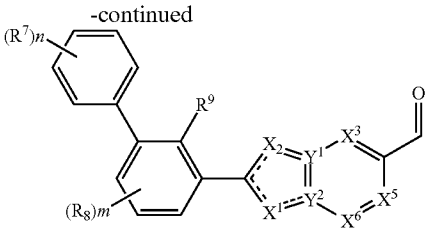

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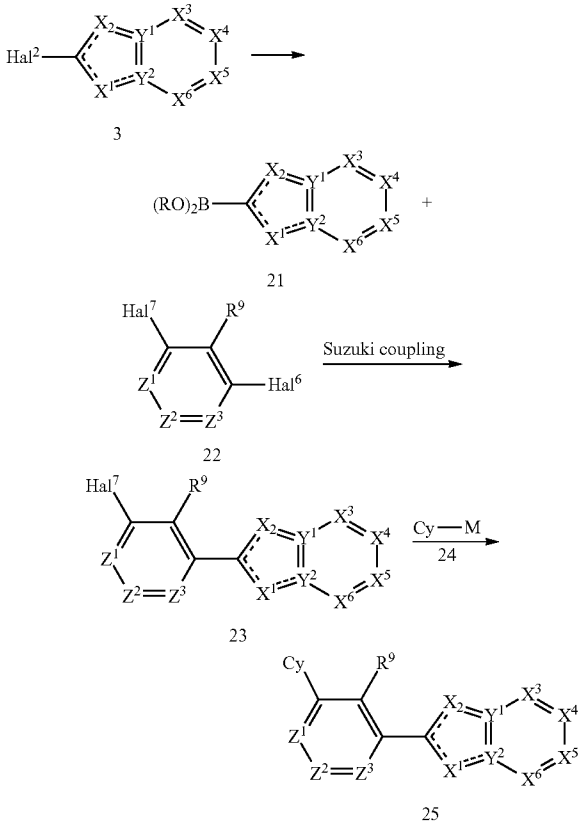
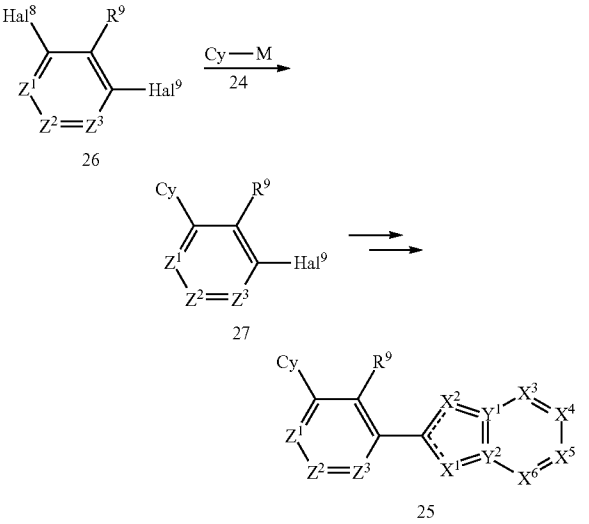
[0209] Alternatively, aldehydes 16 can also be prepared using procedures as shown in Scheme 5, starting from heteroaryl halides 19 (e.g., Hal^5=Cl, Br, I) which can be synthesized according to procedures as described in Scheme 1 or 2. The halide in compounds 19 can be converted to vinyl group to give olefins 20, under standard Suzuki coupling condition (e.g., with vinylboronic acid pinaco ester in the presence of a palladium catalyst and a suitable base). The vinyl group in compounds 20 can be oxidatively cleaved by $NaIO_4$ in the presence of catalytic amount of OsO_4 to form aldehydes 16.

Scheme 6



[0210] Compounds of Formula 25 can be prepared using procedures as outlined in Scheme 6. The halo group (e.g., Hal^2=Cl, Br, I) of heteroaryl compounds 3 can be converted to the boronic esters 21 under standard conditions [e.g., in the presence of bis(pinacolato)diboron and a palladium catalyst, such as, tetrakis(triphenylphosphine) palladium(0), palladium(II) acetate]. Selective coupling of boronates 21 with aryl halides 22 (e.g., Hal^6=Cl, Br, I) under suitable Suzuki coupling condition (e.g., in the presence of a palladium catalyst and a suitable base) can give the N-bridged bicyclic compounds 23. The halide (e.g., Hal^7=Cl, Br, I) in compound 23 can be coupled to compounds of formula 24, 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 25. Alternatively, compound 24 can be a cyclic amine (where M is H and attached to an amine nitrogen in ring Cy) and the coupling of aryl halide 23 with the cyclic amine 24 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 7



[0211] Alternatively, Compounds of Formula 25 can be prepared using the procedures as outlined in Scheme 7. Selective coupling of aryl halides 26 with compounds of formula 24 [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] can be achieved under suitable Suzuki coupling, Stille coupling or Negishi coupling conditions to give compounds of Formula 27. If compound 24 is a cyclic amine (e.g., M is H and attached to nitrogen in ring Cy), the coupling can be achieved under Buchwald amination conditions. Conversion of compound 27 to the final product 25 can be achieved using similar conditions as described in Scheme 1.

III. Uses of the Compounds

[0212] 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 asso-

ciated 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 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') or (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.

[0213] The compounds of the present disclosure inhibit the PD-1/PD-L1 protein/protein interaction, resulting in a PD-1 pathway blockade. The blockade of PD-1 can enhance the immune response to cancerous cells and infectious diseases in mammals, including humans. In some embodiments, the present disclosure provides treatment of an individual or a patient in vivo using a compound of Formula (I') or (I) or a salt or stereoisomer thereof such that growth of cancerous tumors is inhibited. A compound of Formula (I') or (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used to inhibit the growth of cancerous tumors. Alternatively, a compound of Formula (I') or (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used in conjunction with other agents or standard cancer treatments, as described below. In one embodiment, the present disclosure provides a method for inhibiting growth of tumor cells in vitro. The method includes contacting the tumor cells in vitro with a compound of Formula (I') or (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or of a salt or stereoisomer thereof. In another embodiment, the present disclosure provides a method for inhibiting growth of tumor cells in an individual or a patient. The method includes administering to the individual or patient in need thereof a therapeutically effective amount of a compound of Formula (I') or (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.

[0214] In some embodiments, provided herein is a method for treating cancer. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I') or (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.

[0215] Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, endometrial cancer, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers. The compounds of the present disclosure are also useful for the treatment of metastatic cancers, especially metastatic cancers that express PD-L1.

[0216] In some embodiments, cancers treatable with compounds of the present disclosure include melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer, 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.

[0217] In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, solid tumors (e.g., prostate cancer, colon cancer, esophageal cancer, endometrial cancer, ovarian cancer, uterine cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, sarcoma, bladder cancer, etc.), hematological cancers (e.g., lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), DLBCL, mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma or multiple myeloma) and combinations of said cancers.

[0218] PD-1 pathway blockade with compounds of the present disclosure can also be used for treating infections such as viral, bacteria, fungus and parasite infections. The present disclosure provides a method for treating infections such as viral infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I') or (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.

[0219] The present disclosure provides a method for treating bacterial infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I') or (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.

[0220] The present disclosure provides a method for treating fungus infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I') or (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.*

[0221] The present disclosure provides a method for treating parasite infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I') or (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.*

[0222] 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.

[0223] 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.

[0224] 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.

[0225] 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

[0226] 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.

[0227] 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-PR, 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.

[0228] 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.

[0229] In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

[0230] 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.

[0231] 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.

[0232] 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.

[0233] 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.

[0234] 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.

[0235] 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.

[0236] 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).

[0237] 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, mechlorethamine, 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.

[0238] 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.

[0239] The compounds of the present disclosure can further be used in combination with one or more anti-inflammatory agents, steroids, immunosuppressants or therapeutic antibodies.

[0240] The compounds of Formula (I') or (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 cancer-

ous 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.

[0241] The compounds of Formula (I') or (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to express GM-CSF. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). In some embodiments, the compounds of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated from tumor tissue itself. In some embodiments, the compounds of Formula (I') or (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.

[0242] 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.

[0243] 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.

[0244] The compounds of Formula (I') or (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.*

[0245] 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.

[0246] 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.

[0247] 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.*

[0248] 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.*

[0249] 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

[0250] When employed as pharmaceuticals, the compounds of the present disclosure can be administered in the form of pharmaceutical compositions. Thus the present disclosure provides a composition comprising a compound of Formula (I') or (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.

[0251] 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.

[0252] 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.

[0253] 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.

[0254] 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.

[0255] 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.

[0256] 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™).

[0257] 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.

[0258] 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.

[0259] 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.

[0260] 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.

[0261] 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.

[0262] 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.

[0263] 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.

[0264] 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.

[0265] 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.

[0266] 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.

[0267] 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.

[0268] 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.

[0269] 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

[0270] 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.

[0271] 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.

[0272] 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

[0273] The present disclosure also includes pharmaceutical kits useful, e.g., in the treatment or prevention of diseases or disorders associated with the activity of PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80), such as cancer or infections, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I') or (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.

[0274] 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.

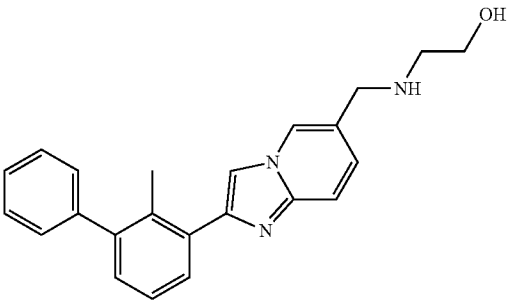
EXAMPLES

[0275] 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

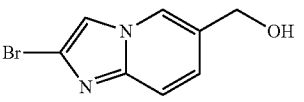
2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl]methyl}amino)ethanol

[0276]



Step 1:
(2-bromoimidazo[1,2-a]pyridin-6-yl)methanol

[0277]

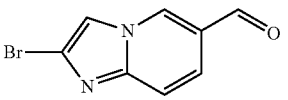


[0278] To a solution of methyl 2-bromoimidazo[1,2-a] pyridine-6-carboxylate (200 mg, 0.784 mmol) (Ark Pharm, cat#AK-31669) in tetrahydrofuran (5.0 mL) at 0° C. was

added 1.0 M diisobutylaluminum hydride in tetrahydrofuran (862 μL, 0.862 mmol). The resulting mixture was stirred at room temperature for 1 h then it was quenched with saturated NH_4Cl aqueous solution (1 mL), stirred for 1 h then filtered through celite. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was used for next step without further purification. LC-MS calculated for $C_8H_8BrN_2O$ $(M+H)^+$: m/z=227.0; found 227.2.

Step 2:
2-bromoimidazo[1,2-a]pyridine-6-carbaldehyde

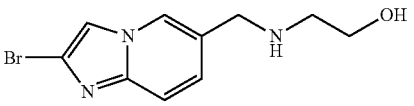
[0279]



[0280] To a suspension of the crude (2-bromoimidazo[1,2-a]pyridin-6-yl)methanol from Step 1 in methylene chloride (5.0 mL) was added Dess-Martin periodinane (499 mg, 1.18 mmol). The resulting mixture was stirred at room temperature for 30 min then quenched with sat'd $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 10% MeOH/DCM to give the desired product (156 mg, 88%). LC-MS calculated for $C_8H_6BrN_2O$ $(M+H)^+$: m/z=225.0; found 225.2.

Step 3: 2-{[(2-bromoimidazo[1,2-a]pyridin-6-yl)methyl]amino}ethanol

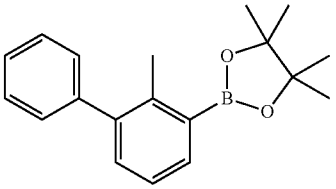
[0281]



[0282] To a solution of 2-bromoimidazo[1,2-a]pyridine-6-carbaldehyde (20 mg, 0.09 mmol) and ethanolamine (7.0 mg, 0.12 mmol) in acetonitrile (1.0 mL) was added sodium triacetoxyborohydride (28 mg, 0.13 mmol). The resulting mixture was stirred at room temperature for overnight then concentrated. The residue was used for next step without further purification. LC-MS calculated for $C_{10}H_{13}BrN_3O$ $(M+H)^+$: m/z=270.0; found 270.2.

Step 4: 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane

[0283]



[0284] A mixture of 3-chloro-2-methylbiphenyl (0.440 mL, 2.47 mmol) (Aldrich, cat#361623), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (1.88 g, 7.40 mmol), palladium acetate (22.2 mg, 0.0987 mmol), K_3PO_4 (1.57 g, 7.40 mmol) and 2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl (101 mg, 0.247 mmol) in 1,4-dioxane (10 mL) was purged with nitrogen then stirred at room temperature for 48 h. The reaction mixture was diluted with dichloromethane (DCM), then washed over water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 5% EtOAc/DCM to give the desired product (656 mg, 90%). LC-MS calculated for $C_{19}H_{24}BO_2$ $(M+H)^+$: m/z=295.2; found 295.2.

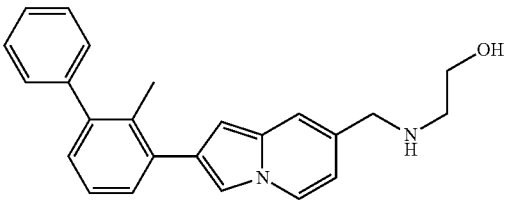
Step 5: 2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl]methyl}amino)ethanol

[0285] To a mixture of 2-{[(2-bromoimidazo[1,2-a]pyridin-6-yl)methyl]amino}ethanol (9 mg, 0.03 mmol), 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane (10 mg, 0.03 mmol) and sodium carbonate (8.58 mg, 0.0809 mmol) in tert-butyl alcohol (0.4 mL) and water (0.2 mL) was added dichloro[1,1'-bis(dicyclohexylphosphino)ferrocene]palladium(II) (3 mg, 0.00324 mmol). The resulting mixture was purged with nitrogen, then heated to 105° C. and stirred for 4 h. The reaction mixture was cooled to room temperature then purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{24}N_3O$ $(M+H)^+$: m/z=358.4; found 358.2.

Example 2

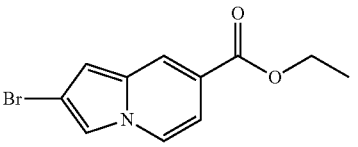
2-({[2-(2-methylbiphenyl-3-yl)indolizin-7-yl]methyl}amino)ethanol

[0286]



Step 1: ethyl 2-bromoindolizine-7-carboxylate

[0287]

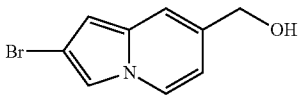


[0288] A mixture of 4-bromo-1H-pyrrole-2-carbaldehyde (Apollo, cat#AS422081: 511 mg, 2.94 mmol), ethyl 4-bromocrotonate (Aldrich, cat#E13830: 1130 mg, 5.87 mmol)

and potassium carbonate (893 mg, 6.46 mmol) in N, N-dimethylformamide (DMF, 8 mL) was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc then washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 30% EtOAc/hexanes to give the desired product as a yellow solid. LC-MS calculated for $C_{11}H_{11}BrNO_2$ $(M+H)^+$: m/z=268.0; found 268.0.

Step 2: (2-bromoindolizin-7-yl)methanol

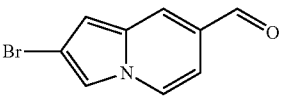
[0289]



[0290] To a solution of ethyl 2-bromoindolizine-7-carboxylate (167 mg, 0.623 mmol) in THF (1 mL) was added lithium tetrahydroaluminate in THF (1.0 M, 400 μL, 0.4 mmol) dropwise at 0° C. The mixture was slowly warmed up to room temperature and stirred for 1 h then the mixture was quenched with EtOAc, followed by water and sodium hydroxide solution. The mixture was extracted with EtOAc three times. The organic phase was combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 60% EtOAc/hexanes to give the desired product. LC-MS calculated for C_9H_9BrNO $(M+H)^+$: m/z=226.0; found 225.9.

Step 3: 2-bromoindolizine-7-carbaldehyde

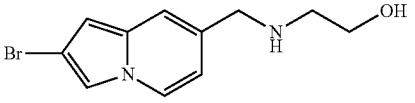
[0291]



[0292] To a solution of (2-bromoindolizin-7-yl)methanol (44.0 mg, 0.195 mmol) in methylene chloride (1.5 mL) was added Dess-Martin periodinane (82.6 mg, 0.195 mmol) at room temperature. The reaction mixture was stirred for 10 min then quenched with $NaHCO_3$ solution and $Na_2S_2O_3$ solution. The mixture was extracted with methylene chloride. The organic phase was combined, dried over $MgSO_4$ and concentrated. The residue was used in the next step without further purification. LC-MS calculated for C_9H_7BrNO $(M+H)^+$: m/z=224.0; found 223.9.

Step 4: 2-{[(2-bromoindolizin-7-yl)methyl]amino}ethanol

[0293]



[0294] To the crude product from Step 3 was added a solution of ethanolamine (23 μL, 0.39 mmol) in methylene chloride (2 mL). The mixture was stirred for 20 min at room temperature then sodium triacetoxyborohydride (82 mg, 0.39 mmol) and acetic acid (1 drop) were added. The mixture was stirred at room temperature for 2 h then quenched by NH_4OH solution and extracted with EtOAc three times. The organic phase was combined, dried over $MgSO_4$ and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{11}H_{14}BrN_{20}O$ $(M+H)^+$: m/z=269.0; found 269.0.

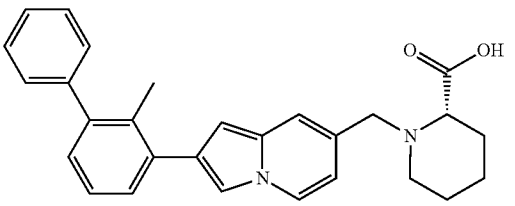
Step 5: 2-({[2-(2-methylbiphenyl-3-yl)indolizin-7-yl]methyl}amino)ethanol

[0295] To a solution of the crude product from Step 4 in 1,4-dioxane (1 mL) and water (0.2 mL) were added 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane (Example 1, Step 4: 57 mg, 0.20 mmol), potassium phosphate (69 mg, 0.32 mmol) and dichloro[1,1'-bis(dicyclohexylphosphino)ferrocene]palladium(II) (10 mg, 0.01 mmol). The resulting mixture was purged with N_2 then stirred at 90° C. for 4 h. The reaction mixture was cooled to room temperature then diluted with EtOAc and washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in MeOH then purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{25}N_2O$ $(M+H)^+$: m/z=357.2; found 357.2.

Example 3

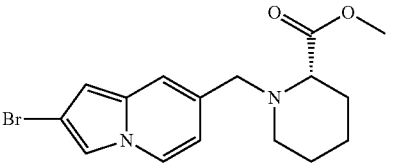
(2S)-1-{[2-(2-methylbiphenyl-3-yl)indolizin-7-yl]methyl}piperidine-2-carboxylic acid

[0296]



Step 1: methyl (2S)-1-[(2-bromoindolizin-7-yl)methyl]piperidine-2-carboxylate

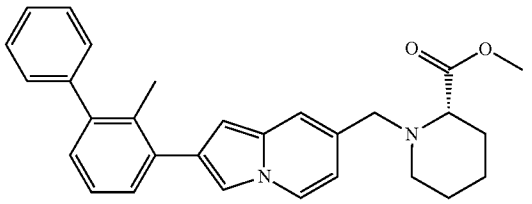
[0297]



[0298] To a mixture of methyl (2S)-piperidine-2-carboxylate hydrogen chloride (180 mg, 1.0 mmol) and 2-bromoindolizine-7-carbaldehyde (75 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) at room temperature was added N,N-diisopropylethylamine (170 μL, 1.0 mmol), followed by acetic acid (100 μL, 2 mmol). The reaction mixture was stirred for 1 h then sodium triacetoxyborohydride (280 mg, 1.3 mmol) was added. After stirring at room temperature for 4 h, the reaction mixture was quenched with NH_4OH solution then extracted with CH_2Cl_2 three times. The organic phase was combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 40% EtOAc/hexanes to give the desired product. LC-MS calculated for $C_{16}H_{20}BrN_2O_2$ $(M+H)^+$: m/z=351.1; found 351.0.

Step 2: methyl (2S)-1-{[2-(2-methylbiphenyl-3-yl) indolizin-7-yl]methyl}piperidine-2-carboxylate

[0299]



[0300] To a solution of methyl (2S)-1-[(2-bromoindolizin-7-yl)methyl]piperidine-2-carboxylate (product from Step 1) in 1,4-dioxane (0.3 mL) and water (0.06 mL) was added 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane (Example 1, Step 4: 18 mg, 0.060 mmol), potassium phosphate (17 mg, 0.078 mmol) and dichloro[1,1'-bis (dicyclohexylphosphino)ferrocene]palladium(II) (2 mg, 0.003 mmol). The mixture was purged with N_2, then heated at 90° C. for 4 h. The reaction mixture was cooled to room temperature, diluted with EtOAc then washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 50% EtOAc/Hexanes to give the desired product. LC-MS calculated for $C_{29}H_{31}N_2O_2$ $(M+H)^+$: m/z=439.2; found 439.2.

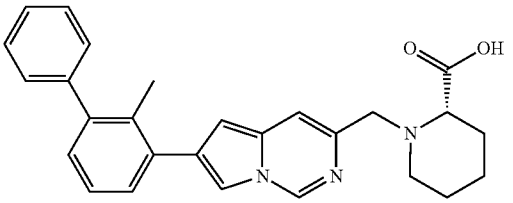
Step 3: (2S)-1-{[2-(2-methylbiphenyl-3-yl)indolizin-7-yl]methyl}piperidine-2-carboxylic acid

[0301] To a mixture of methyl (2S)-1-{[2-(2-methylbiphenyl-3-yl)indolizin-7-yl]methyl}piperidine-2-carboxylate (14 mg, 0.032 mmol) in tetrahydrofuran (THF, 0.3 mL) and MeOH (0.3 mL) was added lithium hydroxide monohydrate (20 mg, 0.4 mmol) and water (0.3 mL). The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with MeOH then purified by prep-HPLC (pH=10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{28}H_{29}N_2O_2$ $(M+H)^+$: m/z=425.2; found 425.2.

Example 4

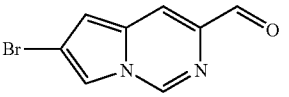
(2 S)-1-{[6-(2-methylbiphenyl-3-yl)pyrrolo[1,2-c] pyrimidin-3-yl]methyl}piperidine-2-carboxylic acid

[0302]



Step 1: 6-bromopyrrolo[1,2-c]pyrimidine-3-carbaldehyde

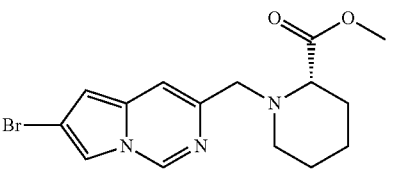
[0303]



[0304] To a solution of ethyl 6-bromopyrrolo[1,2-c]pyrimidine-3-carboxylate (D-L chiral chemicals, cat#ST-KS-041: 119 mg, 0.442 mmol) in CH_2Cl_2 (4 mL) was added diisobutylaluminum hydride in CH_2Cl_2 (1.0 M, 440 μL, 0.44 mmol) dropwise at −78° C. The mixture was slowly warmed up to room temperature and stirred for 3 h. Then the reaction mixture was quenched with EtOAc followed by $(NH_4)_2SO_4$ solution then extracted with EtOAc three times. The organic phase was combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 50% EtOAc/Hexanes to give the desired product. LC-MS calculated for $C_8H_6BrN_2O$ $(M+H)^+$: m/z=225.0; found 224.9.

Step 2: methyl (2S)-1-[(6-bromopyrrolo[1,2-c]pyrimidin-3-yl)methyl]piperidine-2-carboxylate

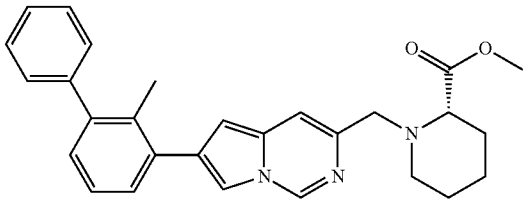
[0305]



[0306] To a solution of 6-bromopyrrolo[1,2-c]pyrimidine-3-carbaldehyde (9.0 mg, 0.040 mmol) and methyl (2S)-piperidine-2-carboxylate [1.0]-hydrogen chloride (18 mg, 0.10 mmol) in CH_2Cl_2 (0.2 mL) were added diisopropylethylamine (17.4 μL, 0.10 mmol) and acetic acid (7 μL, 0.1 mmol) at room temperature. The mixture was stirred for 2 h then sodium triacetoxyborohydride (30 mg, 0.2 mmol) was added. The reaction mixture was stirred at room temperature for 3 h then quenched by NH_4OH solution and extracted with CH_2Cl_2 three times. The organic phase was combined, dried over $MgSO_4$, filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{15}H_{19}BrN_3O_2$ $(M+H)^+$: m/z=352.1; found 352.0.

Step 3: Methyl (2S)-1-{[6-(2-methylbiphenyl-3-yl) pyrrolo[1,2-c]pyrimidin-3-yl]methyl}piperidine-2-carboxylate

[0307]



[0308] To the mixture of the crude product from Step 2 in 1,4-dioxane (0.3 mL) and water (0.07 mL) was added 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane (Example 1, Step 4: 21 mg, 0.070 mmol), potassium phosphate (20. mg, 0.092 mmol) and dichloro[1,1'-bis (dicyclohexylphosphino) ferrocene]palladium(II) (3 mg, 0.004 mmol). The mixture was purged with N_2, then heated at 90° C. for 4 h. The reaction mixture was cooled to room temperature, diluted with EtOAc then washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 60% EtOAc/hexanes to give the desired product. LC-MS calculated for $C_{28}H_{30}N_3O_2$ $(M+H)^+$: m/z=440.2; found 440.2.

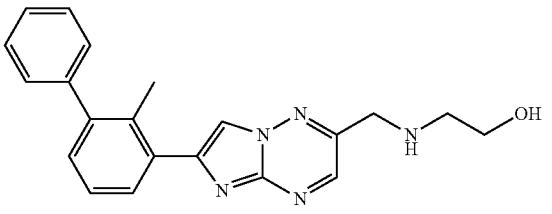
Step 4: (2S)-1-{[6-(2-methylbiphenyl-3-yl)pyrrolo [1,2-c]pyrimidin-3-yl]methyl}piperidine-2-carboxylic acid

[0309] To a solution of methyl (2S)-1-{[6-(2-methylbiphenyl-3-yl)pyrrolo[1,2-c]pyrimidin-3-yl] methyl}piperidine-2-carboxylate (6.7 mg, 0.015 mmol) in THF (0.1 mL) and MeOH (0.1 mL) was added lithium hydroxide monohydrate (8 mg, 0.2 mmol) and water (0.1 mL). The resulting mixture was stirred at room temperature overnight then diluted with MeOH and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{27}H_{28}N_3O_2$ $(M+H)^+$: m/z=426.2; found 426.2.

Example 5

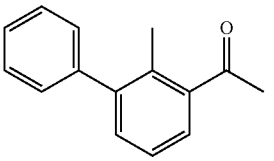
2-((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4] triazin-2-yl)methylamino)ethanol

[0310]



Step 1: 1-(2-methylbiphenyl-3-yl)ethanone

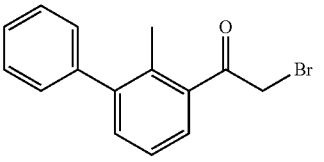
[0311]



[0312] To a solution of 1-(3-bromo-2-methylphenyl)ethanone (AstaTech, cat#CL9266: 4.2 g, 20. mmol) in water (10 mL) and 1,4-dioxane (45 mL) were added potassium phosphate (8.4 g, 39 mmol), phenylboronic acid (2.6 g, 22 mmol) and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1, 1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.8 g, 1 mmol). The resulting mixture was purged with nitrogen then stirred at 100° C. for 30 mins. The reaction mixture was cooled to room temperature then diluted with ethyl acetate, washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, then concentrated. The residue was purified by silica gel chromatography eluting with 0-50% ethyl acetate in hexanes to afford the desired product (3.95 g, 95%) as light yellowish oil. LC-MS calculated for $C_{15}H_{15}O$ $(M+H)^+$: m/z=211.3; found 211.3.

Step 2: 2-bromo-1-(2-methylbiphenyl-3-yl)ethanone

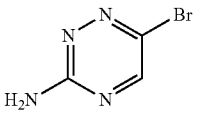
[0313]



[0314] To a solution of 1-(2-methylbiphenyl-3-yl)ethanone (1.25 g, 5.94 mmol) in ethyl acetate (30 mL) was added copper(II) bromide (5.3 g, 24 mmol). The reaction mixture was stirred at 80° C. for 2 hours then cooled to room temperature, filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography using 0-50% ethyl acetate in hexanes to afford desired product (1.51 g, 87%) as light yellowish oil. LC-MS calculated for $C_{15}H_{14}BrO$ $(M+H)^+$: m/z=289.0; found 289.0.

Step 3: 6-bromo-1,2,4-triazin-3-amine

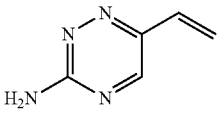
[0315]



[0316] To a solution of 1,2,4-triazin-3-amine (Aldrich, cat#100625: 5.0 g, 52 mmol) in acetonitrile (50 mL) and water (70 mL) was added N-bromosuccinimide (9.72 g, 54.6 mmol). The resulting mixture was stirred at room temperature for 2 hours then diluted with 100 mL saturated $NaHCO_3$ solution, and stirred for another 1 hour, then extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ then filtered and concentrated to dryness to afford the desired product (4.5 g, 49%) as a brownish solid, which was used for the next step without further purification.

Step 4: 6-vinyl-1,2,4-triazin-3-amine

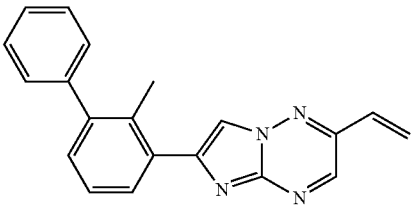
[0317]



[0318] To a solution of 6-bromo-1,2,4-triazin-3-amine (1.0 g, 5.7 mmol) in water (3 mL) and 1,4-dioxane (17 mL) were added potassium phosphate (2.4 g, 11 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, cat#633348: 0.97 g, 6.3 mmol) and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.09 g, 0.1 mmol). The resulting mixture was purged with nitrogen then stirred at 80° C. for 30 mins. The reaction mixture was cooled to room temperature, diluted with ethyl acetate then washed with water and brine. Then organic layer was dried over $MgSO_4$, filtered, then concentrated to dryness to afford the desired product (580 mg, 83%) as a brownish solid which was used for next step without further purification.

Step 5: 6-(2-methylbiphenyl-3-yl)-2-vinylimidazo[1,2-b][1,2,4]triazine

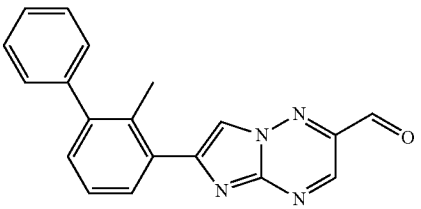
[0319]



[0320] To a solution of 6-vinyl-1,2,4-triazin-3-amine (200 mg, 2 mmol) in isopropyl alcohol (6.3 mL) was added 2-bromo-1-(2-methylbiphenyl-3-yl)ethanone (470 mg, 1.6 mmol). The resulting mixture was warmed up to 90° C. and stirred for 2 hours. The reaction mixture was cooled to room temperature then concentrated to dryness. The residue was purified by silica gel chromatography using 0-50% ethyl acetate in hexanes to afford desired product (200 mg, 40%) as a yellowish solid. LC-MS calculated for $C_{20}H_{17}N_4$ $(M+H)^+$: m/z=313.1; found 313.4.

Step 6: 6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazine-2-carbaldehyde

[0321]



[0322] To a solution of 6-(2-methylbiphenyl-3-yl)-2-vinylimidazo[1,2-b][1,2,4]triazine (340 mg, 1.1 mmol) in tetrahydrofuran (10 mL) and water (20 mL) was added potassium osmate, dihydrate (80 mg, 0.2 mmol) and sodium periodate (880 mg, 4.1 mmol). The resulting mixture was stirred at room temperature for 2 hours then diluted with ethyl acetate, washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, then concentrated to dryness. The residue was purified by silica gel chromatography using 0-80% ethyl acetate in hexanes to afford the desired product (220 mg, 64%) as a yellowish solid. LC-MS calculated for $C_{19}H_{15}N_4O$ $(M+H)^+$: m/z=315.1; found 315.2.

Step 7: 2-((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methylamino)ethanol

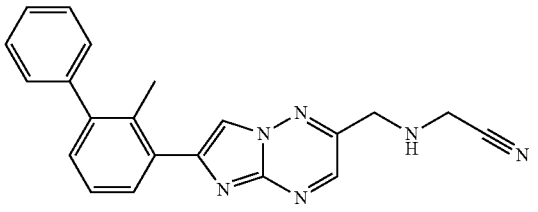
[0323] To a solution of 6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazine-2-carbaldehyde (20 mg, 0.06 mmol) in N,N-dimethylformamide (500 μL) was added ethanolamine (19 μL, 0.32 mmol) and acetic acid (18 μL, 0.32 mmol). The resulting mixture was stirred at room temperature for 30 min

then sodium cyanoborohydride (8.0 mg, 0.13 mmol) was added. The mixture was stirred at room temperature for 2 hours then diluted with methanol and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{22}N_5O$ $(M+H)^+$: m/z=360.2; found 360.2.

Example 6

2-((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methylamino)acetonitrile

[0324]

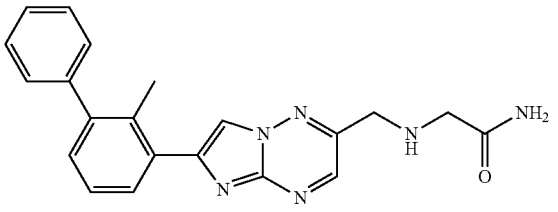


[0325] This compound was prepared using similar procedures as described for Example 5 with aminoacetonitrile replacing ethanolamine in Step 7. The resulting mixture was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{19}N_6$ $(M+H)^+$: m/z=355.2; found 355.2.

Example 7

2-((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methylamino)acetamide

[0326]

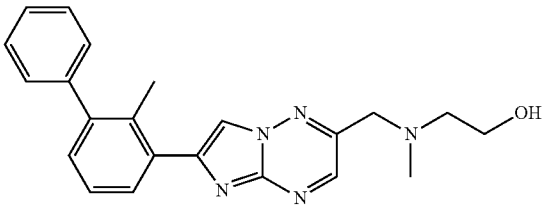


[0327] This compound was prepared using similar procedures as described for Example 5 with glycinamide replacing ethanolamine in Step 7. The resulting mixture was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{21}N_6O$ $(M+H)^+$: m/z=373.2; found 373.2.

Example 8

2-(methyl((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methyl)amino)ethanol

[0328]

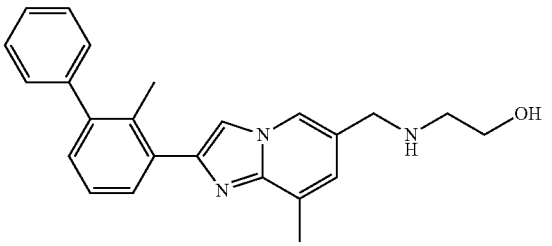


[0329] This compound was prepared using similar procedures as described for Example 5 with 2-(methylamino) ethanol replacing ethanolamine in Step 7. The resulting mixture was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{24}N_5O$ $(M+H)^+$: m/z=374.2; found 374.2.

Example 9

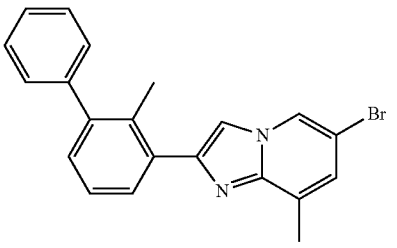
2-((8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl)methylamino)ethanol

[0330]



Step 1: 6-bromo-8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridine

[0331]

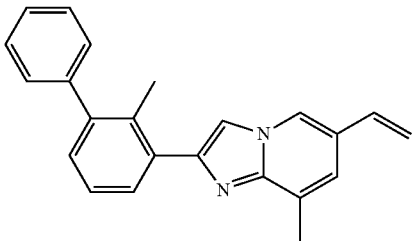


[0332] To a solution of 2-bromo-1-(2-methylbiphenyl-3-yl)ethanone (Example 5, Step 2: 500 mg, 2 mmol) in

isopropyl alcohol (7 mL) was added 5-bromo-3-methylpyridin-2-amine (Aldrich, cat#525537: 320 mg, 1.7 mmol). The resulting mixture was stirred at 90° C. for 1 hour then cooled to room temperature and concentrated to dryness. The residue was purified by silica gel chromatography using 0-60% ethyl acetate in hexanes to afford the desired product (299 mg, 40%) as a white solid. LC-MS calculated for $C_{21}H_{18}BrN_2$ $(M+H)^+$: m/z=377.1; found 377.0.

Step 2: 8-methyl-2-(2-methylbiphenyl-3-yl)-6-vinylimidazo[1,2-a]pyridine

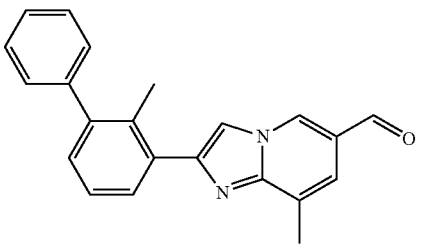
[0333]



[0334] To a solution of 6-bromo-8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridine (229 mg, 0.607 mmol) in water (0.5 mL) and 1,4-dioxane (2.5 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, cat#633348: 100 mg, 0.67 mmol), potassium phosphate (0.26 g, 1.2 mmol) and (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphoranylidene]palladium (0.05 g, 0.06 mmol). The mixture was purged with nitrogen then stirred at 90° C. for 1 hour. The reaction mixture was cooled to room temperature then concentrated. The residue was purified by silica gel chromatography using 0-60% ethyl acetate in hexanes to afford the desired product (197 mg, 82%) as a yellowish solid. LC-MS calculated for $C_{23}H_{21}N_2$ $(M+H)^+$: m/z=325.2; found 325.1.

Step 3: 8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridine-6-carbaldehyde

[0335]



[0336] To a solution of 8-methyl-2-(2-methylbiphenyl-3-yl)-6-vinylimidazo[1,2-a]pyridine (162 mg, 0.499 mmol) in 1,4-dioxane (3.5 mL) and water (6 mL) was added potassium osmate, dihydrate (20 mg, 0.05 mmol) and sodium metaperiodate (210 mg, 1.0 mmol). The resulting mixture was stirred at room temperature for 2 hours then diluted with water, quenched with sodium sulfite, then extracted with ethyl acetate. The combined extract was dried over Na_2SO_4, filtered, then concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography using 0-80% ethyl acetate in hexanes to afford the desired product (57 mg, 35%) as a yellowish solid. LC-MS calculated for $C_{22}H_{19}N_2O$ $(M+H)+$: m/z=327.1; found 327.1.

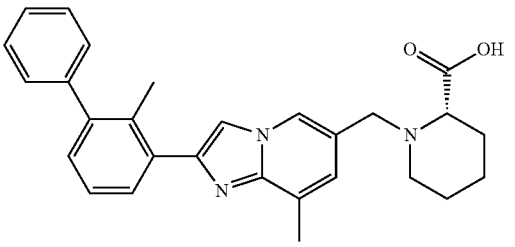
Step 4: 2-((8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl)methylamino) ethanol

[0337] To a solution of 8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridine-6-carbaldehyde (28 mg, 0.086 mmol) in N,N-dimethylformamide (700 μL) was added ethanolamine (10. μL, 0.17 mmol) and acetic acid (50 μL, 0.8 mmol). The mixture was stirred at room temperature overnight then sodium cyanoborohydride (0.027 g, 0.43 mmol) was added. The reaction mixture was stirred at room temperature for another 30 mins then diluted with methanol and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford desired product as TFA salt. LC-MS calculated for $C_{24}H_{26}N_3O$ $(M+H)+$: m/z=372.2; found 372.2.

Example 10

(S)-1-((8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl)methyl)piperidine-2-carboxylic acid

[0338]

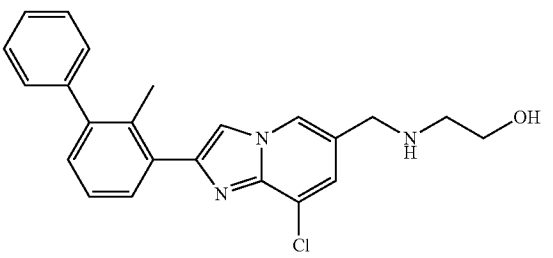


[0339] This compound was prepared using similar procedures as described for Example 9 with (S)-piperidine-2-carboxylic acid replacing ethanolamine in Step 4. The resulting mixture was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{30}N_3O_2$ $(M+H)^+$: m/z=440.2; found 440.3.

Example 11

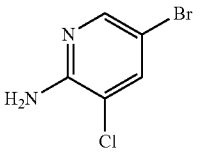
2-((8-chloro-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl)methylamino)ethanol

[0340]



Step 1: 5-bromo-3-chloropyridin-2-amine

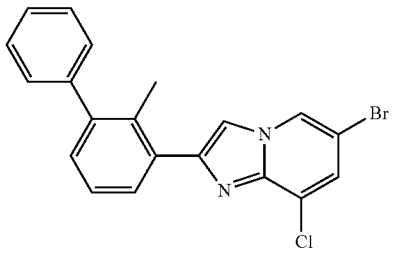
[0341]



[0342] To a solution of 2-amino-5-bromopyridine (Aldrich, cat#122858: 5.0 g, 29 mmol) in N,N-dimethylformamide (60 mL) was added N-chlorosuccinimide (4.2 g, 32 mmol). The resulting mixture was stirred at room temperature for 1 hour then saturated $NaHCO_3$ aqueous solution was added. The mixture was stirred for 10 min then extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography using 0-100% ethyl acetate in hexanes to afford the desired product (4.8 g, 80%) as a yellowish solid. LC-MS calculated for $C_5H_5BrClN_2$ $(M+H)^+$: m/z=206.9; found 206.9.

Step 2: 6-bromo-8-chloro-2-(2-methylbiphenyl-3-yl) imidazo[1,2-a]pyridine

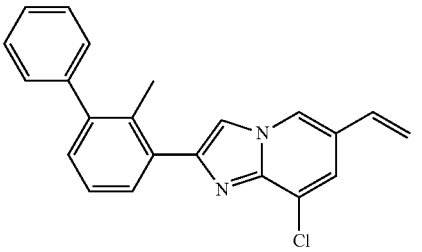
[0343]



[0344] To a solution of 2-bromo-1-(2-methylbiphenyl-3-yl)ethanone (Example 5, Step 2: 560 mg, 1.9 mmol) in isopropyl alcohol (7 mL) was added 5-bromo-3-chloropyridin-2-amine (400 mg, 2 mmol). The resulting mixture was stirred at 90° C. for 4 hours then cooled to room temperature and concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography using 0-50% ethyl acetate in hexanes to afford the desired product (82 mg, 10%) as a yellowish solid. LC-MS calculated for $C_{20}H_{15}BrClN_2$ $(M+H)^+$: m/z=397.0; found 397.0.

Step 3: 8-chloro-2-(2-methylbiphenyl-3-yl)-6-vinylimidazo[1,2-a]pyridine

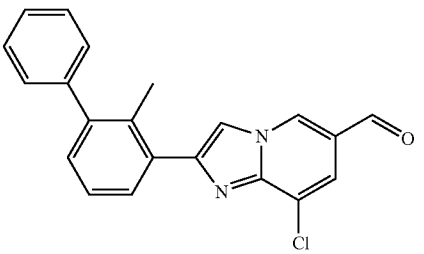
[0345]



[0346] To a solution of 6-bromo-8-chloro-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridine (82 mg, 0.21 mmol) in water (0.2 mL) and 1,4-dioxane (2 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, cat#633348: 35 mg, 0.23 mmol), potassium phosphate (88 mg, 0.41 mmol) and (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphoranylidene]palladium (8 mg, 0.01 mmol). The resulting mixture was purged with nitrogen then warmed up to 70° C. and stirred for 30 mins. The reaction mixture was then cooled to room temperature, diluted with brine, and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and then concentrated to dryness under reduced pressure. The residue was purified with silica gel chromatography using 0-80% ethyl acetate in hexanes to afford the desired product (59 mg, 83%) as a yellowish solid. LC-MS calculated for $C_{22}H_{18}ClN_2$ $(M+H)^+$: m/z=345.1; found 345.0.

Step 4: 8-chloro-2-(2-methylbiphenyl-3-yl)imidazo [1,2-a]pyridine-6-carbaldehyde

[0347]



[0348] To a solution of 8-chloro-2-(2-methylbiphenyl-3-yl)-6-vinylimidazo[1,2-a]pyridine (59 mg, 83%) in 1,4-dioxane (2 mL,) and water (3 mL) was added sodium periodate (0.13 g, 0.62 mmol) and potassium osmate dihydrate (20 mg, 0.04 mmol). The resulting mixture was stirred at room temperature for 2 hours then diluted with water, quenched with sodium sulfite, and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure.

The residue was used for next step without further purification. LC-MS calculated for $C_{21}H_{16}ClN_2O$ $(M+H)^+$: m/z=347.1; found 347.0.

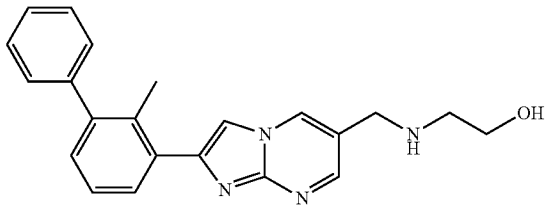
Step 5: 2-((8-chloro-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl)methylamino) ethanol

[0349] To a solution of the crude product from Step 4 in N,N-dimethylformamide (2 mL) was added ethanolamine (50 μL, 0.82 mmol) and acetic acid (0.2 mL, 3.5 mmol). The resulting mixture was stirred at room temperature overnight then sodium cyanoborohydride (0.065 g, 1.0 mmol) was added. The mixture was stirred at room temperature for another 30 mins then diluted with methanol and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford desired product as the TFA salt. LC-MS calculated for $C_{23}H_{23}ClN_3O$ $(M+H)^+$: m/z=392.2; found 392.1.

Example 12

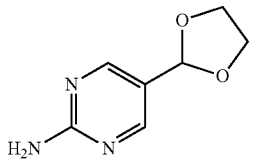
2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrimidin-6-yl]methyl}amino)ethanol

[0350]



Step 1: 5-(1,3-dioxolan-2-yl)pyrimidin-2-amine

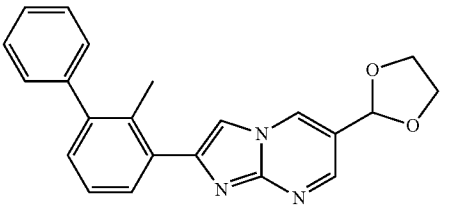
[0351]



[0352] To a solution of 2-aminopyrimidine-5-carbaldehyde (Aldrich, cat#734845: 200 mg, 1.62 mmol) in toluene (5 mL) were added 1,2-ethanediol (120 μL, 2.1 mmol) and p-toluenesulfonic acid monohydrate (30 mg, 0.2 mmol), followed by molecular sieves (400 mg). The mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated to dryness under reduced pressure and the residue was used in the next step without further purification. LC-MS calculated for $C_7H_{10}N_3O_2$ $(M+H)^+$: m/z=168.1; found 168.0.

Step 2: 6-(1,3-dioxolan-2-yl)-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrimidine

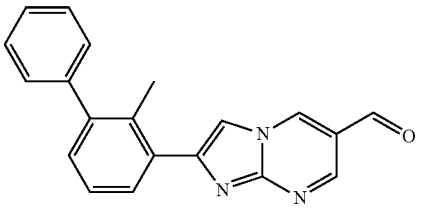
[0353]



[0354] To a solution of 2-bromo-1-(2-methylbiphenyl-3-yl)ethanone (Example 5, Step 2: 138 mg, 0.48 mmol) in isopropyl alcohol (2 mL) was added 5-(1,3-dioxolan-2-yl) pyrimidin-2-amine (80. mg, 0.48 mmol) and dipotassium hydrogen phosphate (170 mg, 0.96 mmol). The reaction mixture was stirred at 110° C. overnight. The mixture was then cooled to room temperature, poured into water and extracted with dichloromethane twice (20 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 25% ethyl acetate/DCM to give the desired product. LC-MS calculated for $C_{22}H_{20}N_3O_2$ $(M+H)^+$: m/z=358.2; found 358.1.

Step 3: 2-(2-methylbiphenyl-3-yl)imidazo[1,2-a] pyrimidine-6-carbaldehyde

[0355]



[0356] To a solution of 6-(1,3-dioxolan-2-yl)-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrimidine (40 mg, 0.1 mmol) in tetrahydrofuran (2 mL) was added 1.0 M hydrogen chloride in water (450 μL, 0.45 mmol). The reaction solution was stirred at 50° C. for 2 hour then cooled to room temperature, diluted with DCM, washed with $NaHCO_3$ aqueous solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{20}H_{16}N_3O$ $(M+H)^+$: m/z=314.1; found 314.1.

Step 4: 2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrimidin-6-yl]methyl}amino)ethanol

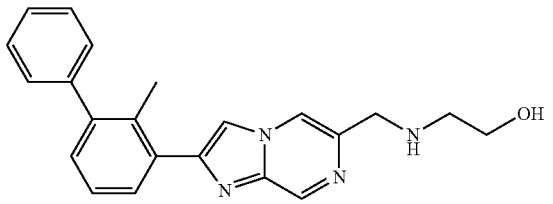
[0357] To a solution of 2-(2-methylbiphenyl-3-yl)imidazo [1,2-a]pyrimidine-6-carbaldehyde (15.0 mg, 0.0479 mmol) in 1,2-dichloroethane (1 mL) was added ethanolamine (5.8

μL, 0.096 mmol). The mixture was stirred at room temperature for 30 min, then sodium triacetoxyborohydride (30 mg, 0.14 mmol) was added. The resulting mixture was stirred at room temperature overnight then concentrated. The residue was diluted with MeOH and purified by prep-HPLC (pH=10, acetonitrile/water+NH_4OH) to give the desired product. LC-MS calculated for $C_{22}H_{23}N_4O$ $(M+H)^+$: m/z=359.2; found 359.1.

Example 13

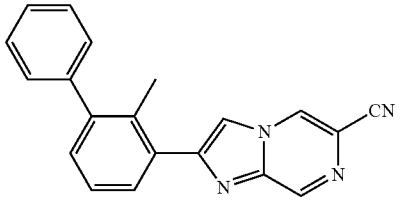
2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazin-6-yl]methyl}amino)ethanol

[0358]



Step 1: 2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazine-6-carbonitrile

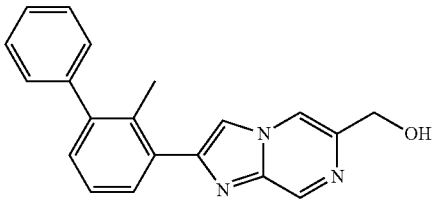
[0359]



[0360] To a solution of 2-bromo-1-(2-methylbiphenyl-3-yl)ethanone (Example 5, Step 2: 782 mg, 2.71 mmol) in isopropyl alcohol (10 mL) was added 5-aminopyrazine-2-carbonitrile (Ark Pharm, cat#AK-21935: 325. mg, 2.71 mmol). The resulting mixture was heated at 110° C. overnight then cooled to room temperature and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 25% ethyl acetate/DCM to give the desired product. LC-MS calculated for $C_{20}H_{15}N_4$ $(M+H)^+$: m/z=311.1; found 311.1.

Step 2: [2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazin-6-yl]methanol

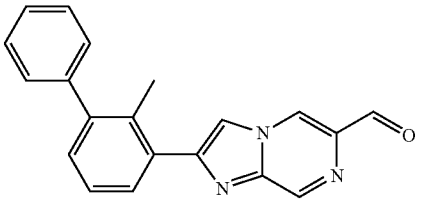
[0361]



[0362] To a solution of 2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazine-6-carbonitrile (110 mg, 0.35 mmol) in methylene chloride (3 mL) was added 1.0 M diisobutylaluminum hydride in DCM (0.71 mL, 0.71 mmol) dropwise at −78° C. The mixture was stirred at −78° C. for 2 hours then quenched with a few drops of saturated NH_4Cl aqueous solution and diluted with saturated sodium potassium tartrate solution. The suspension was stirred at room temperature overnight then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 25% ethyl acetate/DCM to give the desired product. LC-MS calculated for $C_{20}H_{18}N_3O$ $(M+H)^+$: m/z=316.1; found 316.1.

Step 3: 2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazine-6-carbaldehyde

[0363]



[0364] Dimethyl sulfoxide (27 μL, 0.38 mmol) was added to a solution of 2.0 M oxalyl chloride in DCM (0.095 mL, 0.19 mmol) in methylene chloride (1 mL) at −78° C. To the above solution, [2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazin-6-yl]methanol (30. mg, 0.095 mmol) in methylene chloride (1 mL) was slowly added and then continued to stir at −78° C. for 30 mins. Then N,N-diisopropylethylamine (0.13 mL, 0.76 mmol) was added. The reaction mixture was slowly warmed to 0° C. then poured into $NaHCO_3$ aqueous solution and extracted with DCM. The combined extracts were washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 0 to 25% ethyl acetate/DCM to give the desired product. LC-MS calculated for $C_{20}H_{16}N_3O$ $(M+H)^+$: m/z=314.1; found 314.1.

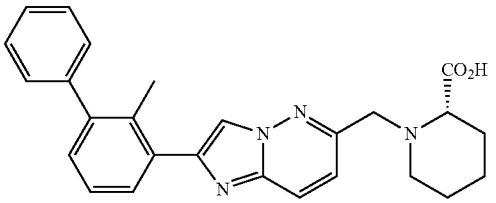
Step 4: 2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazin-6-yl]methyl}amino)ethanol

[0365] To a solution of 2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazine-6-carbaldehyde (15.0 mg, 0.0479 mmol) in 1,2-dichloroethane (1 mL) was added N,N-diisopropylethylamine (17 μL, 0.096 mmol) and ethanolamine (5.8 μL, 0.096 mmol). The mixture was stirred at room temperature for 20 min, then sodium triacetoxyborohydride (30. mg, 0.14 mmol) was added. The reaction mixture was stirred at room temperature for 3 h then concentrated. The residue was dissolved in MeOH then purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{23}N_4O$ $(M+H)^+$: m/z=359.2; found 359.1.

Example 14

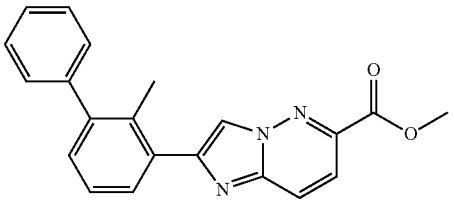
(S)-1-((2-(2-methylbiphenyl-3-yl)imidazo[1,2-b] pyridazin-6-yl)methyl)piperidine-2-carboxylic acid

[0366]



Step 1: methyl 2-(2-methylbiphenyl-3-yl)imidazo[1, 2-b]pyridazine-6-carboxylate

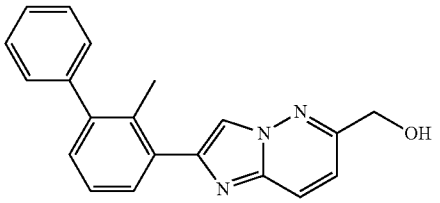
[0367]



[0368] Methyl 6-aminopyridazine-3-carboxylate (Accela ChemBio, cat#SY006049: 87 mg, 0.57 mmol) was added to the solution of 2-bromo-1-(2-methylbiphenyl-3-yl)ethanone (Example 5, Step 2: 181 mg, 0.626 mmol) in isopropyl alcohol (2.3 mL). The mixture was stirred at 90° C. for 2 h then cooled to room temperature and concentrated. The residue was purified by chromatography (15-30% EtOAc/ hexanes) on silica gel to give the desired product 85 mg (43% yield). LC-MS calculated for $C_{21}H_{18}N_3O_2$ $(M+H)^+$: m/z=344.1; found: 344.1.

Step 2: [2-(2-methylbiphenyl-3-yl)imidazo[1,2-b] pyridazin-6-yl]methanol

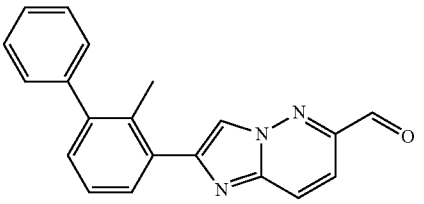
[0369]



[0370] 1.0 M Diisobutylaluminum hydride in DCM (0.33 mL, 0.33 mmol) was added to a solution of methyl 2-(2-methylbiphenyl-3-yl)imidazo[1,2-b]pyridazine-6-carboxylate (104 mg, 0.303 mmol) in methylene chloride (1.5 mL) at −40° C. The mixture was warmed to −5° C. and stirred for 40 min and then stirred at room temperature overnight. The mixture was quenched with aqueous NH_4Cl and potassium sodium tartrate, and extracted with DCM. The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (90-100% EtOAc) on silica gel to give the desire product (35 mg). LC-MS calculated for $C_{20}H_{18}N_3O$ $(M+H)^+$: m/z=316.1; found: 316.1.

Step 3: 2-(2-methylbiphenyl-3-yl)imidazo[1,2-b] pyridazine-6-carbaldehyde

[0371]



[0372] Dess-Martin periodinane (66.6 mg, 0.157 mmol) was added to the solution of [2-(2-methylbiphenyl-3-yl) imidazo[1,2-b]pyridazin-6-yl]methanol (33.0 mg, 0.105 mmol) in DCM (3 mL). The mixture was stirred at room temperature for 15 min then quenched with aqueous sodium bisulfate and extracted with Et_2O. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (20-30% EtOAc/Hex) on silica gel to give the desired product (24 mg). LC-MS calculated for $C_{20}H_{16}N_3O$ $(M+H)^+$: m/z=314.1; found: 314. 1.

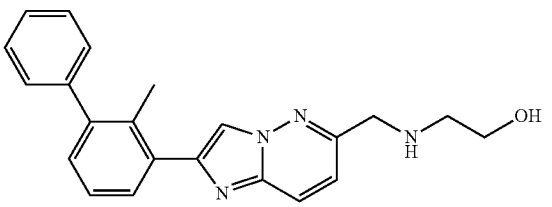
Step 4: (2S)-1-{[2-(2-methylbiphenyl-3-yl)imidazo [1,2-b]pyridazin-6-yl]methyl}piperidine-2-carboxylic acid

[0373] (2S)-piperidine-2-carboxylic acid (26.8 mg, 0.207 mmol) was added to a solution of 2-(2-methylbiphenyl-3-yl)imidazo[1,2-b]pyridazine-6-carbaldehyde (13.0 mg, 0.0415 mmol) in N,N-dimethylformamide (0.41 mL), followed by acetic acid (3.54 μL, 0.0622 mmol). The reaction mixture was stirred at room temperature for 10 min. Then sodium cyanoborohydride (7.9 mg, 0.12 mmol) was added. The reaction mixture was stirred at room temperature overnight then diluted with MeOH and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{27}N_4O_2$ $(M+H)^+$: m/z=427.2; found: 427.2.

Example 15

2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-b] pyridazin-6-yl]methyl}amino)ethanol

[0374]

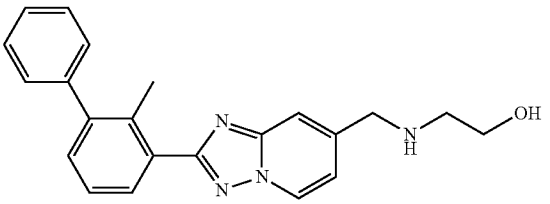


[0375] This compound was prepared using similar procedures as described for Example 14 with ethanolamine replacing (2S)-piperidine-2-carboxylic acid in Step 4. The resulting mixture was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{23}N_4O$ $(M+H)^+$: m/z=359.2; found 359.2.

Example 16

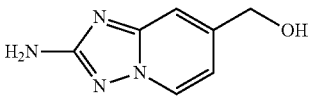
2-({[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]methyl}amino)ethanol

[0376]



Step 1: (2-amino[1,2,4]triazolo[1,5-a]pyridin-7-yl)methanol

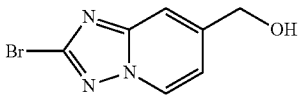
[0377]



[0378] Ethoxycarbonyl isothiocyanate (606 μL, 5.36 mmol) was added to a solution of (2-aminopyridin-4-yl)methanol (Aldrich, cat#714577: 555 mg, 4.47 mmol) in 1,4-dioxane (22.4 mL). The reaction mixture was stirred at room temperature for 15 h. The mixture was concentrated and the residue was dissolved in methanol (16.0 mL)/ethanol (16.0 mL), then N,N-diisopropylethylamine (1.56 mL, 8.94 mmol) was added, followed by hydroxylamine hydrochoride (932 mg, 13.4 mmol). The reaction mixture was stirred at 45° C. for 2 h then cooled to room temperature and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_7H_9N_4O$ $(M+H)^+$: m/z=165.1; found: 165.1.

Step 2: (2-bromo[1,2,4]triazolo[1,5-a]pyridin-7-yl)methanol

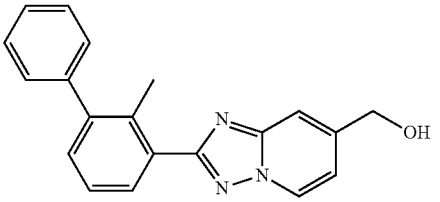
[0379]



[0380] tert-Butyl nitrite (1.28 mL, 10.7 mmol) was added to a suspension of (2-amino[1,2,4]triazolo[1,5-a]pyridin-7-yl)methanol (734 mg, 4.47 mmol) and copper(II) bromide (2.00 g, 8.94 mmol) in acetonitrile (55 mL). The reaction mixture was stirred at room temperature for 2 h then diluted with DCM and washed with water. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give the desired product as a yellow solid (842 mg, 83% yield). LC-MS calculated for $C_7H_7BrN_3O$ $(M+H)^+$: m/z=228.0; found: LC/MS: 228.0.

Step 3: [2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]methanol

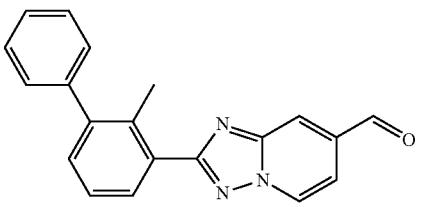
[0381]



[0382] A mixture of (2-bromo[1,2,4]triazolo[1,5-a]pyridin-7-yl)methanol (128 mg, 0.564 mmol), 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane (Example 1, Step 4: 199 mg, 0.676 mmol), (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphoranylidene]palladium (44.4 mg, 0.0564 mmol) and K_3PO_4 (215 mg, 1.01 mmol) in 1,4-dioxane (2.6 mL)/water (0.3 mL) was purged with nitrogen then stirred at 90° C. for 18 h. The mixture was cooled to room temperature then diluted with DCM, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (40-100% EtOAc/hexanes) on silica gel to give the desired product as an off-white solid (85.0 mg). LC-MS calculated for $C_{20}H_{18}N_3O$ $(M+H)^+$: m/z=316.1; found: 316.1.

Step 4: 2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridine-7-carbaldehyde

[0383]



[0384] Dess-Martin periodinane (80.7 mg, 0.190 mmol) was added to the solution of [2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]methanol (40.0 mg, 0.127 mmol) in dichloromethane (3 mL). The mixture was stirred at room temperature for 1.5 h and more Dess-Martin periodinane (1.5 equiv) was added. The mixture was stirred for another 3.5 h then quenched with aqueous sodium bisulfate and extracted with dichloromethane. The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified with chromatography on silica gel to give the desired product (29 mg). LC-MS calculated for $C_{20}H_{16}N_3O$ $(M+H)^+$: m/z=314.1; found: 314.1.

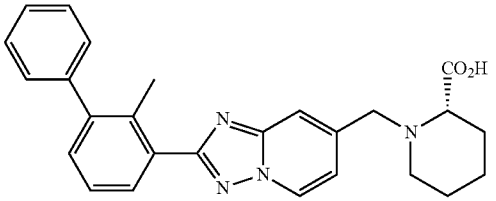
Step 5: 2-({[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]methyl}amino)ethanol

[0385] Ethanolamine (7.3 mg, 0.12 mmol) was added to a solution of 2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridine-7-carbaldehyde (7.5 mg, 0.024 mmol) in N,N-dimethylformamide (0.24 mL), followed by acetic acid (2.0 μL, 0.036 mmol). The reaction mixture was stirred at room temperature for 10 min then sodium cyanoborohydride (4.5 mg, 0.072 mmol) was added. The mixture was stirred at room temperature overnight then diluted with MeOH and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{23}N_4O$ $(M+H)^+$: m/z=359.2; found: 359.2.

Example 17

(2S)-1-{[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]methyl}piperidine-2-carboxylic acid

[0386]

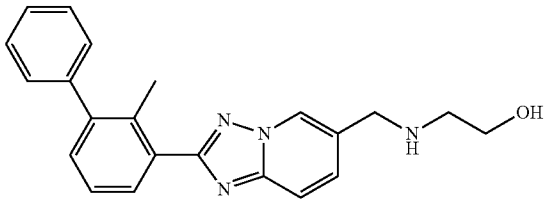


[0387] This compound was prepared using similar procedures as described for Example 16 with (2S)-piperidine-2-carboxylic acid replacing ethanolamine in Step 5. The resulting mixture was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{27}N_4O_2$ $(M+H)^+$: m/z=427.2; found 427.2.

Example 18

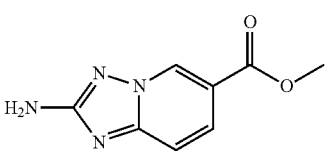
2-({[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}amino)ethanol

[0388]



Step 1: methyl 2-amino[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

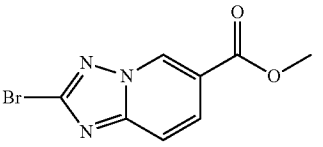
[0389]



[0390] To a solution of methyl 6-aminonicotinate (Aldrich, cat#648736: 699 mg, 4.59 mmol) in 1,4-dioxane (23.0 mL) was added ethoxycarbonyl isothiocyanate (623 μL, 5.51 mmol). The reaction mixture was stirred at room temperature for 15 h. The crude was concentrated and the residue was dissolved in methanol (17 mL)/ethanol (17 mL) then N,N-diisopropylethylamine (1.6 mL, 9.2 mmol) was added, followed by hydroxyaminehydrochoride (958 mg, 13.8 mmol). The resulting mixture was stirred at 45° C. for 2 h then cooled to room temperature and concentrated. The residue was directly used for the next step without further purification. LC-MS calculated for $C_8H_9N_4O_2$ $(M+H)^+$: m/z=193.1; found: 193.0.

Step 2: methyl 2-bromo[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

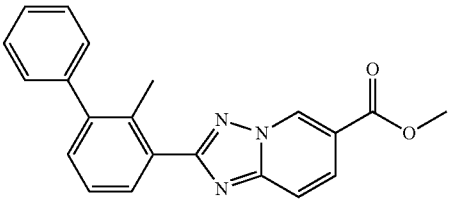
[0391]



[0392] tert-Butyl nitrite (1.31 mL, 11.0 mmol) was added to a suspension of methyl 2-amino[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (883 mg, 4.59 mmol) and copper(II) bromide (2.05 g, 9.19 mmol) in acetonitrile (44 mL). The mixture was stirred at room temperature for 2 h then diluted with dichloromethane and washed with water. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give the desired product as a white solid (483 mg, 41% yield). LC-MS calculated for $C_8H_7BrN_3O_2$ $(M+H)^+$: m/z=256.0; found: 256.0.

Step 3: methyl 2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

[0393]

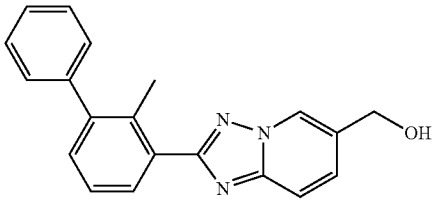


[0394] A mixture of methyl 2-bromo[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (188 mg, 0.734 mmol), 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane (Example 1, Step 4: 259 mg, 0.881 mmol), (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphoranylidene]palladium (57.8 mg, 0.0734 mmol) and K_3PO_4 (280 mg, 1.32 mmol) in 1,4-dioxane (3.4 mL)/water (0.3 mL) was purged with nitrogen then stirred at 90° C. for 15 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by chromatography (20-25% EtOAc/Hex) on silica gel to give

the desired product as an off-white solid (188 mg, 75% yield). LC-MS calculated for $C_{21}H_{18}N_3O_2$ $(M+H)^+$: 344.1; found: 344.1.

Step 4: [2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methanol

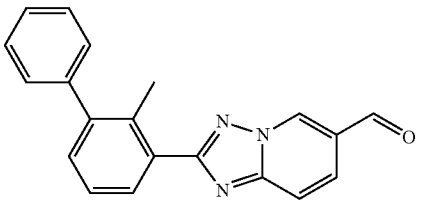
[0395]



[0396] Diisobutylaluminum hydride in DCM (643 μL, 0.643 mmol) was added to the solution of methyl 2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (184 mg, 0.536 mmol) in Et_2O (5 mL) at 0° C. The mixture was stirred at room temperature for 3 h then another portion of diisobutylaluminum hydride (1M in DCM, 1 mL, 1 mmol) was added. The mixture was stirred at room temperature for another 2 h then quenched with aqueous NH_4Cl and stirred with Rochelle salt, and then extracted with DCM. The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (50-100% EtOAc) on silica gel to give the desired product (86 mg, 51% yield). LC-MS calculated for $C_{20}H_{18}N_3O$ $(M+H)^+$: 316.1; found: 316.1.

Step 5: 2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridine-6-carbaldehyde

[0397]



[0398] Dess-Martin periodinane (171 mg, 0.404 mmol) was added to a solution of [2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methanol (85 mg, 0.27 mmol) in dichloromethane (3 mL). The mixture was stirred at room temperature for 1 h then quenched with aqueous sodium bisulfate, and extracted with dichloromethane. The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified with chromatography (20-40% EtOAc/Hex) on silica gel to give the desired product (70 mg). LC-MS calculated for $C_{20}H_{16}N_3O$ $(M+H)^+$: m/z=314.1; found: 314.1.

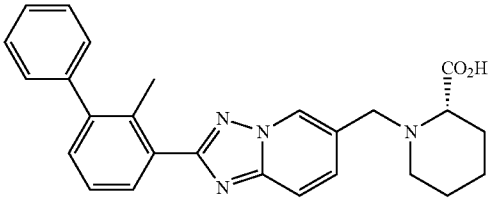
Step 6: 2-({[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}amino)ethanol

[0399] Ethanolamine (8.7 μL, 0.15 mmol) was added to a solution of 2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridine-6-carbaldehyde (9.0 mg, 0.029 mmol) in N,N-dimethylformamide (0.28 mL), followed by acetic acid (2.5 μL, 0.04 mmol). The reaction mixture was stirred at room temperature for 10 min then sodium cyanoborohydride (5.4 mg, 0.087 mmol) was added. The mixture was stirred at room temperature overnight then diluted with MeOH and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{23}N_4O$ $(M+H)^+$: m/z=359.2; found: 359.2.

Example 19

(2S)-1-{[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}piperidine-2-carboxylic acid

[0400]

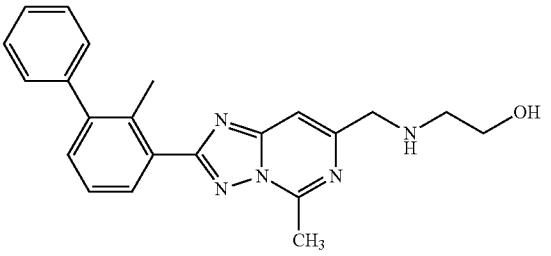


[0401] The title compound was prepared using similar procedures as described for Example 18 with (2S)-piperidine-2-carboxylic acid replacing ethanolamine in Step 6. The resulting mixture was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{27}N_4O_2$ $(M+H)^+$: m/z=427.2; found 427.2.

Example 20

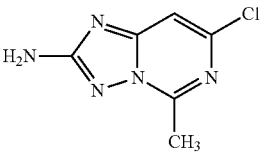
2-({[5-methyl-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-c]pyrimidin-7-yl]methyl}amino)ethanol

[0402]



Step 1: 7-chloro-5-methyl[1,2,4]triazolo[1,5-c]pyrimidin-2-amine

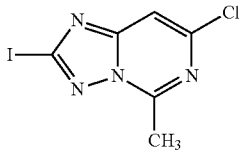
[0403]



[0404] To a solution of 6-chloro-2-methylpyrimidin-4-amine (AK Scientific, cat#W3822: 585 mg, 4.07 mmol) in 1,4-dioxane (20.4 mL) was added ethoxycarbonyl isothiocyanate (553 μL, 4.89 mmol). The reaction mixture was heated at 50° C. for 6 h then cooled to room temperature and concentrated. The residue was dissolved in methanol (15 mL)/ethanol (15 mL) then N,N-diisopropylethylamine (1.42 mL, 8.15 mmol) was added, followed by hydroxylamine hydrochoride (849 mg, 12.2 mmol). The mixture was stirred at 50° C. for 3 h then cooled to room temperature and concentrated. The residue was directly used for the next step without further purification. LC-MS calculated for $C_6H_7ClN_5$ $(M+H)^+$: m/z=184.0; found 184.0.

Step 2: 7-chloro-2-iodo-5-methyl[1,2,4]triazolo[1,5-c]pyrimidine

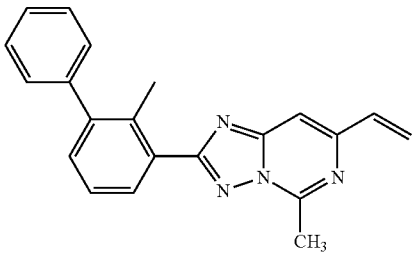
[0405]



[0406] tert-Butyl nitrite (1.16 mL, 9.78 mmol) was added to a suspension of 7-chloro-5-methyl[1,2,4]triazolo[1,5-c]pyrimidin-2-amine (crude product from Step 1) and copper (I) iodide (1.55 g, 8.15 mmol) in acetonitrile (39.4 mL). The mixture was heated at 70° C. for 2 h then cooled to room temperature, diluted with dichloromethane and washed with water. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give the desired product as a yellow solid (61.0 mg). LC-MS calculated for $C_6H_5ClN_4$ $(M+H)^+$: m/z=294.9; found 294.9.

Step 3: 5-methyl-2-(2-methylbiphenyl-3-yl)-7-vinyl[1,2,4]triazolo[1,5-c]pyrimidine

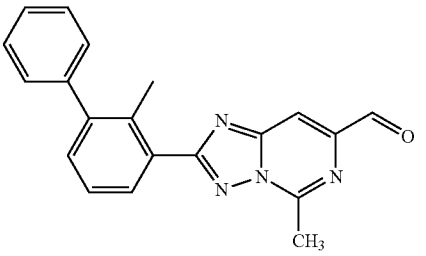
[0407]



[0408] A mixture of 7-chloro-2-iodo-5-methyl[1,2,4]triazolo[1,5-c]pyrimidine (61 mg, 0.21 mmol), 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-dioxaborolane (Example 1, Step 4: 67 mg, 0.23 mmol), (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphoranylidene]palladium (16 mg, 0.02 mmol) and K_3PO_4 (79 mg, 0.37 mmol) in 1,4-dioxane (0.96 mL)/water (75 μL) was purged with nitrogen then heated at 90° C. for 3 h. The reaction mixture was cooled to room temperature then 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (105 μL, 0.62 mmol) was added, followed by (2'-aminobiphenyl-2-yl)(chloro)[dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphoranylidene]palladium (16 mg, 0.02 mmol) and K_3PO_4 (79 mg, 0.37 mmol). The mixture was purged with nitrogen again and stirred at 90° C. for 3 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane then dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (8-15% EtOAc/Hex) on silica gel to give the desired product as an off-white solid. LC-MS calculated for $C_{21}H_{19}N_4$ $(M+H)^+$: m/z=327.2; found 327.1.

Step 4: 5-methyl-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-c]pyrimidine-7-carbaldehyde

[0409]



[0410] Potassium osmate dihydrate (0.96 mg, 0.0026 mmol) and sodium periodate (5.85 mg, 0.0273 mmol) were added to the solution of 5-methyl-2-(2-methylbiphenyl-3-yl)-7-vinyl[1,2,4]triazolo[1,5-c]pyrimidine (8.5 mg, 0.026 mmol) in tetrahydrofuran (0.07 mL) and water (0.11 mL). The mixture was stirred at room temperature for 1 h then diluted with ethyl acetate and washed with water. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was directly used for the next step without further purification. LC-MS calculated for $C_{20}H_{17}N_4O$ $(M+H)^+$: m/z=329.1; found 329.2.

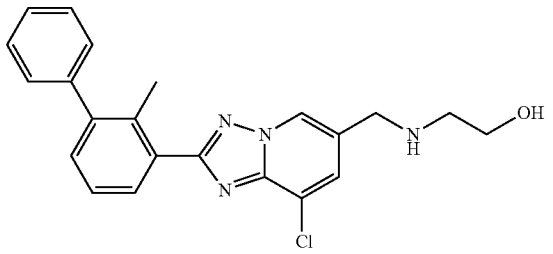
Step 5: 2-({[5-methyl-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-c]pyrimidin-7-yl]methyl}amino)ethanol

[0411] Ethanolamine (5.9 μL, 0.097 mmol) was added to the solution of 5-methyl-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-c]pyrimidine-7-carbaldehyde (6.4 mg, 0.019 mmol) in N,N-dimethylformamide (0.19 mL), followed by acetic acid (1.7 μL, 0.029 mmol). The mixture was stirred at room temperature for 10 min then sodium cyanoborohydride (3.7 mg, 0.059 mmol) was added. The mixture was stirred at room temperature overnight then diluted with MeOH and purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{24}N_5O$ $(M+H)^+$: m/z=374.2; found: 374.2.

Example 21

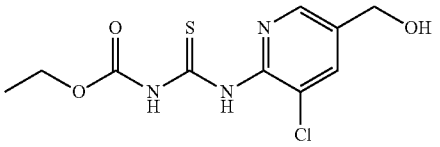
2-({[8-chloro-2-(2-methylbiphenyl-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}amino)ethanol

[0412]



Step 1: ethyl ({[3-chloro-5-(hydroxymethyl)pyridin-2-yl]amino}carbonothioyl)carbamate

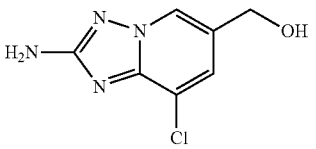
[0413]



[0414] To a solution of (6-amino-5-chloropyridin-3-yl) methanol (551 mg, 3.47 mmol) in 1,4-dioxane (8.8 mL) was added ethoxycarbonyl isothiocyanate (471 μL, 4.17 mmol). The reaction mixture was stirred at room temperature for 15 h. The precipitate was filtered and washed with dichloromethane. The mother liquor was concentrated and filtered again. Two crops of the solid were collected and dried to give the desired product 599 mg (60% yield). LC-MS calculated for $C_{10}H_{13}ClN_3O_3S$ $(M+H)^+$: m/z=290.0; found: 290.0.

Step 2: (2-amino-8-chloro[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanol

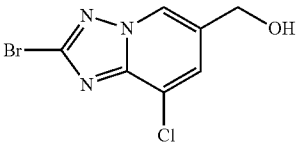
[0415]



[0416] Hydroxyaminehydrochloride (423 mg, 6.09 mmol) was added to a solution of ethyl ({[3-chloro-5-(hydroxymethyl)pyridin-2-yl]amino}carbonothioyl)carbamate (588 mg, 2.03 mmol) in methanol (7.5 mL)/ethanol (7.5 mL), followed by N,N-diisopropylethylamine (0.707 mL, 4.06 mmol). The reaction mixture was then heated at 50° C. for 1.5 h. The crude was concentrated. The residue was directly used in the next step. LC-MS calculated for $C_7H_8ClN_4O$ $(M+H)^+$: m/z=199.0; found: 199.0.

Step 3: (2-bromo-8-chloro[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanol

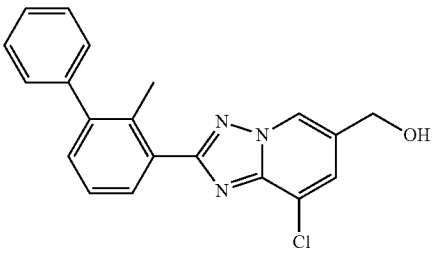
[0417]



[0418] tert-Butyl nitrite (579 μL, 4.87 mmol) was added to a suspension of (2-amino-8-chloro[1,2,4]triazolo[1,5-a] pyridin-6-yl)methanol (403 mg, 2.03 mmol) and copper(II) bromide (906 mg, 4.06 mmol) in acetonitrile (19.6 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane and washed with water. The organic phase was dried, filtered and concentrated. The residue was purified by chromatography on silica gel (50-75% EtOAc/Hex) to give the desired product as a white solid (428 mg, 82% yield, two steps). LC-MS calculated for $C_7H_6BrClN_3O$ $(M+H)^+$: m/z=261.9; found: 261.9.

Step 4: [8-chloro-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methanol

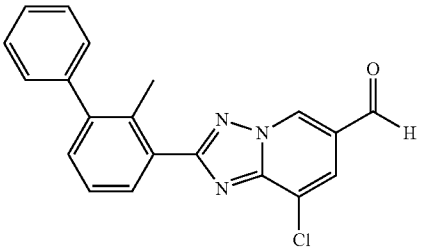
[0419]



[0420] A mixture of (2-bromo-8-chloro[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanol (350 mg, 1.33 mmol), 4,4,5,5-tetramethyl-2-(2-methylbiphenyl-3-yl)-1,3,2-di oxaborolane (Example 1, Step 4: 392 mg, 1.33 mmol), K_3PO_4 (509 mg, 2.40 mmol) and tetrakis(triphenylphosphine)palladium (0) (385 mg, 0.333 mmol) in 1,4-dioxane (6.18 mL)/water (480 μL) was stirred and heated at 110° C. for 4 h. The crude mixture was dried over a drying agent and filtered. The filtrate was concentrated. The residue was purified by chromatography (40-60% EtOAc/Hex) on silica gel to give the desired product 291 mg (63% yield). LC-MS calculated for $C_{20}H_{17}ClN_3O$ $(M+H)^+$: m/z=350.1; found: 350.1.

Step 5: 8-chloro-2-(2-methylbiphenyl-3-yl)[1,2,4] triazolo[1,5-a]pyridine-6-carbaldehyde

[0421]



[0422] Dess-Martin periodinane (706 mg, 1.66 mmol) was added to a solution of [8-chloro-2-(2-methylbiphenyl-3-yl) [1,2,4]triazolo[1,5-a]pyridin-6-yl]methanol (291 mg, 0.832 mmol) in dichloromethane (3.94 mL). The mixture was stirred at room temperature for 1 h. The mixture was quenched with aq. sodium bisulfate and extracted with dichloromethane. The organic phase was dried over a drying agent and filtered. The filtrate was concentrated. The residue was purified by chromatography (15-25% EtOAc/Hex) on silica gel to give the desired product (215 mg, 74% yield) as a white solid. LC-MS calculated for $C_{20}H_{15}ClN_3O$ $(M+H)^+$: m/z=348.1; found: 348.1.

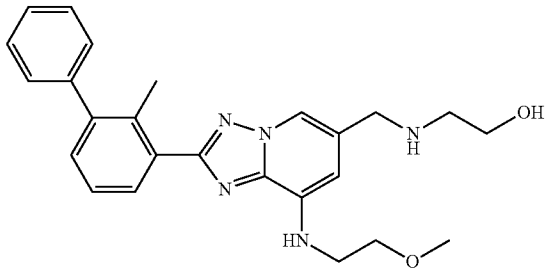
Step 6: 2-({[8-chloro-2-(2-methylbiphenyl-3-yl)[1,2, 4]triazolo[1,5-a]pyridin-6-yl]methyl}amino)ethanol

[0423] Ethanolamine (186 μL, 3.09 mmol) was added to a solution of 8-chloro-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridine-6-carbaldehyde (215 mg, 0.618 mmol) in N,N-dimethylformamide (3.87 mL), followed by trifluoroacetic acid (143 μL). The reaction mixture was stirred at room temperature for 10 min. Then sodium cyanoborohydride (116 mg, 1.85 mmol) was added. The reaction mixture was stirred at room temperature overnight. The crude was diluted with water and extracted with dichloromethane. The organic phase was concentrated. The residue was purified by chromatography on silica gel (5-15% MeOH/DCM) to give the desired product 188 mg (77% yield). LC-MS calculated for $C_{22}H_{22}ClN_4O$ $(M+H)^+$: m/z=393.1; found: 393.1.

Example 22

2-({[8-[(2-methoxyethyl)amino]-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl] methyl}amino)ethanol

[0424]

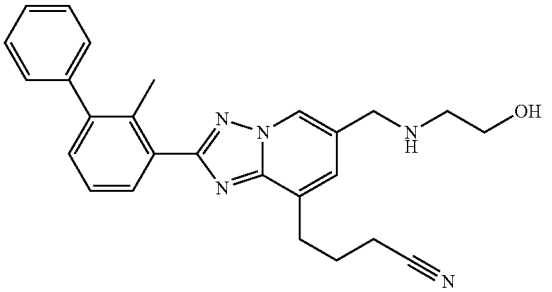


[0425] [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4', 6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate methanesulfonate (Brettphos-Pd-G3, Aldrich, cat#761605: 3.7 mg, 0.0041 mmol) was added to a mixture of 2-({[8-chloro-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl] methyl}amino)ethanol (8.0 mg, 0.020 mmol), cesium carbonate (13.3 mg, 0.0407 mmol) and 2-methoxyethylamine (5.3 μL, 0.061 mmol) in 1,4-dioxane (152 μL). The mixture was stirred at 100° C. for 45 min. The crude was diluted with MeOH and filtered. The filtrate was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford the desired product as the TFA salt. LC-MS calculated for $C_{25}H_{30}N_5O_2$ $(M+H)^+$: m/z=432.2; found: 432.2.

Example 23

4-[6-{[(2-hydroxyethyl)amino]methyl}-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-8-yl] butanenitrile

[0426]

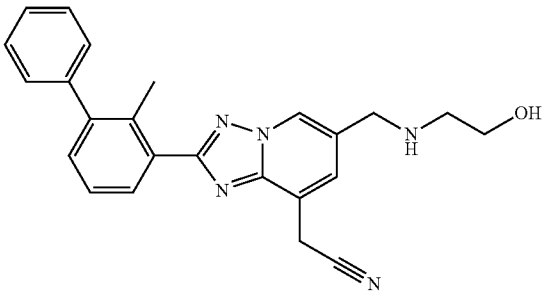


[0427] Chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (RuPhos-Pd-G2, Aldrich, cat#753246: 1.6 mg, 0.0020 mmol) was added to a mixture of 2-({[8-chloro-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl] methyl}amino)ethanol (Example 21: 8.0 mg, 0.02 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanenitrile (7.9 mg, 0.041 mmol) and cesium carbonate (13.3 mg, 0.0407 mmol) in 1,4-dioxane (94.5 μL)/water (31.1 μL). The mixture was stirred at 100° C. for 1 h. The crude was diluted with MeOH and filtered. The filtrate was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{28}N_5O$ $(M+H)^+$: m/z=426.2; found: 426.3.

Example 24

[6-{[(2-hydroxyethyl)amino]methyl}-2-(2-methyl biphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-8-yl] acetonitrile

[0428]

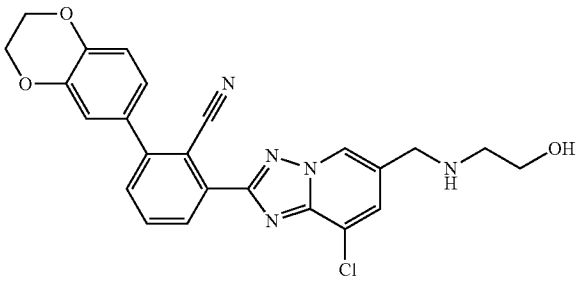


[0429] Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos-Pd-G2, Aldrich, cat#741825: 4.8 mg, 0.0061 mmol) was added to a mixture of 2-({[8-chloro-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}amino) ethanol (Example 21: 12.0 mg, 0.0305 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (8.94 mg, 0.0458 mmol) and potassium phosphate (19.4 mg, 0.0916 mmol) in 1,4-dioxane (188 μL, 2.41 mmol)/water (11.0 μL, 0.611 mmol). The mixture was stirred at 100° C. for 2 h. The crude was diluted with MeOH and filtered through Celite. The filtrate was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to afford the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{24}N_5O$ $(M+H)^+$: m/z=398.2; found: 398.2.

Example 25

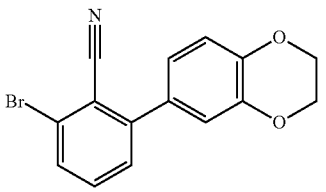
2-(8-chloro-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile

[0430]



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

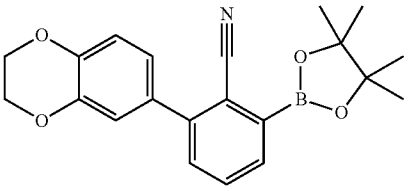
[0431]



[0432] A mixture of 2-bromo-6-iodobenzonitrile (3.01 g, 9.78 mmol), 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (1.60 g, 8.89 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1) (363 mg, 0.444 mmol) and potassium carbonate (3.07 g, 22.2 mmol) in 1,4-dioxane (36.0 mL, 462 mmol) and water (1.60 mL, 88.9 mmol) was degassed and recharged with nitrogen. The mixture was then heated and stirred at 75° C. for 4 h. The reaction mixture was dried over a drying agent and filtered. The filtrate was concentrated. The residue was purified by chromatography on silica gel (10-15% EtOAc/Hex) to afford the desired product 1.48 g. LC-MS calculated for $C_{15}H_{11}BrNO_2$ $(M+H)^+$: m/z=316.0 and 318.0; found: 316.0 and 318.0.

Step 2: 2-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

[0433]



[0434] A mixture of 2-bromo-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile (1.20 g, 3.80 mmol), Bis(pinacolato) diboron (1.06 g, 4.18 mmol), [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (150 mg, 0.19 mmol), potassium acetate (1.1 g, 11 mmol) in 1,4-dioxane (30 mL, 400 mmol) was degassed for 5 min, and then stirred at 90° C. for 4 h. The crude was diluted with dichloromethane and then filtered. The filtrate was concentrated. The residue was purified by chromatography on silica gel to afford the desired product. LC-MS calculated for $C_{21}H_{23}BNO_4$ $(M+H)^+$: m/z=364.2; found: 364.2.

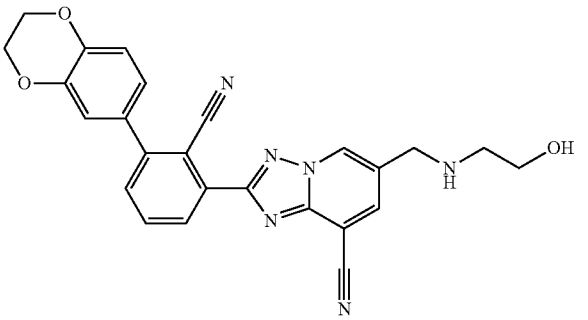
Step 3: 2-(8-chloro-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile

[0435] This compound was prepared using similar procedures as described for Example 21. The resulting crude was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{21}ClN_5O_3$ $(M+H)^+$: m/z=462.1; found: 462.1.

Example 26

2-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile

[0436]



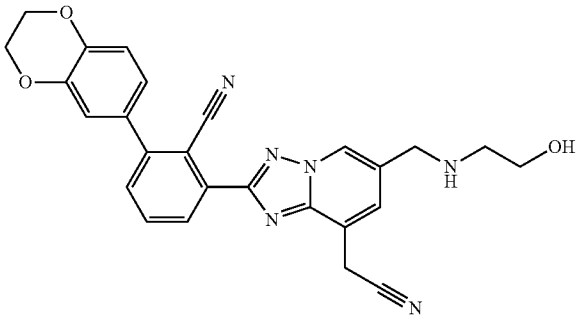
[0437] A mixture of 2-(8-chloro-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)-6-(2,3-di-

hydro-1,4-benzodioxin-6-yl)benzonitrile (Example 25: 6.0 mg, 0.013 mmol), potassium hexacyanoferrate(II) trihydrate (5.49 mg, 0.0130 mmol), and potassium acetate (0.255 mg, 0.00260 mmol) in 1,4-dioxane (32.2 μL)/water (32.2 μL) was stirred and heated at 100° C. for 1 h. The resulting crude was diluted with MeOH and filtered. The filtrate was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{25}H_{21}N_6O_3$ $(M+H)^+$: m/z=453.2; found: 453.2.

Example 27

2-(8-(cyanomethyl)-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile

[0438]



[0439] This compound was prepared using similar procedures as described for Example 24. The resulting crude was purified by prep-HPLC (pH=2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{23}N_6O_3$ $(M+H)^+$: m/z=467.2; found: 467.2.

Example A. PD-1/PD-L1 Homogeneous Time-Resolved Fluorescence (HTRF) Binding Assay

[0440] 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 pre-incubated 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.

[0441] Compounds of the present disclosure, as exemplified in Examples 1-20, showed IC_{50} values in the following ranges: +=IC_{50}≤100 nM; ++=100 nM<IC_{50}≤500 nM; +++=500 nM<IC_{50}≤10000 nM

[0442] 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.

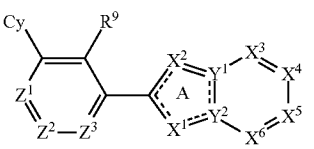
TABLE 1

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	+
22	++
23	+
24	+
25	+
26	+
27	+

[0443] 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:

one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;

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;

X^5 is N or CR^5;

X^6 is N or CR^6;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents;

Z^1 is N or CR^{8a};

Z^2 is N or CR^{8b};

Z^3 is N or CR^{8c};

R^1, R^2, R^{8c}, R^{8b} and R^{8c} are each independently selected from H, C, alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, CN, OR^{10}, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, NH_2, —NHR^{10}, —$NR^{10}R^{10}$, $NHOR^{10}$, $C(O)R^{10}$, $C(O)NR^{10}R^{10}$, $C(O)OR^{10}$, $OC(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{10}$, $NR^{10}C(O)NR^{10}R^{10}$, $C(=NR^{10})R^{10}$, $C(=NR^{10})NR^{10}R^{10}$, $NR^{10}C(=NR^{10})NR^{10}R^{10}$, $NR^{10}S(O)R^{10}$, $NR^{10}S(O)_2R^{10}$, $NR^{10}S(O)_2NR^{10}R^{10}$, $S(O)R^{10}$, $S(O)NR^{10}R^{10}$, $S(O)_2R^{10}$, and $S(O)_2NR^{10}R^{10}$, wherein each R^{10} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-4} alkyl-, C_{6-10} aryl, C_{6-10} aryl-C_{1-4} alkyl-, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^1, R^2, R^{8a}, R^{8b}, R^{8c} and R^{10} are each optionally substituted with 1, 2 or 3 independently selected R^b substituents;

R^9 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^9 are each optionally substituted with 1, 2 or 3 R^b substituents;

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

R^3, R^4, R^5, R^6 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^3, R^4, R^5, R^6 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^h substituents, with the proviso that at least one of R^3, R^4, R^5 and R^6 is other than H;

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

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^h 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^e, $C(O)R^c$, $C(O)NR^cR^c$, $C(O)OR^c$, $OC(O)R^c$, $OC(O)NR^cR^c$, $C(=NR^c)NR^cR^c$, $NR^cC(=NR^c)NR^cR^c$, 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, $NHOR^o$, OR^o, SR^o, $C(O)R^o$, $C(O)NR^oR^o$, $C(O)OR^o$, $OC(O)R^oOC(O)NR^oR^o$, 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 R^p substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, halo, CN, $NHOR^r$, OR^r, SR^r, $C(O)R^r$, $C(O)NR'R^r$, $C(O)OR^r$, $OC(O)R^r$, $OC(O)NR'R^r$, NHR^r, $NR'R^r$, $NR'C(O)R^r$, $NR'C(O)NR'R^r$, $NR'C(O)OR^r$, $C(=NR')NR'R^r$, $NR'C(=NR')NR'R^r$, $NR'C(=NOH)NR'R^r$, $NR'C(=NCN)NR'R^r$, $S(O)R^r$, $S(O)NR'R^r$, $S(O)_2R^r$, $NR'S(O)_2R^r$, $NR'S(O)_2NR'R^r$ and $S(O)_2NR'R^r$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-10 membered heteroaryl)-C_{1-4} alkyl- and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

or any two R^a substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^h substituents independently selected from C_{1-6} alkyl, C_{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_{2-6} alkenyl, C_{2-6} alkynyl, 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- 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, CN, $NHOR^k$, OR^k, SR^k, $C(O)R^k$, $C(O)NR^kR^k$, $C(O)OR^k$, $OC(O)R^k$, $OC(O)NR^kR^k$, NHR^k, NR^kR^k, $NR^kC(O)R^k$, $NR^kC(O)NR^kR^k$, $NR^kC(O)OR^k$, $C(=NR^k)NR^kR^k$, $NR^kC(=NR^k)NR^kR^k$, $S(O)R^k$, $S(O)NR^kR^k$, $S(O)_2R^k$, $NR^kS(O)_2R^k$, $NR^kS(O)_2NR^kR^k$, and $S(O)_2NR^kR^k$, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} 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^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^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, 4-7 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, 4-7 membered heterocycloalkyl, 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^{12}, $NR^{12}R^{12}$, 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^{12} is independently C_{1-6} alkyl;

⋯ is a single bond or a double bond to maintain ring A being aromatic; and

with the proviso that the compound is other than 6-(6-chloro-3-methylimidazol[1,2-a]pyridine-2-yl)-4-(4-chlorophenyl)-(1,1-dimethylethoxy)-2,5-dimethyl-3-pyridineacetic acid or 6-(6-chloroimidazol[1,2-a]pyridine-2-yl)-4-(4-chlorophenyl)-(1,1-dimethylethoxy)-2,5-dimethyl-3-pyridineacetic acid, or enantiomers thereof.

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

one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;

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;

X^5 is N or CR^5;

X^6 is N or CR^6;

Cy is C_{6-10} aryl, C_{3-10} cycloalkyl, 5- to 14-membered heteroaryl, or 4- to 10-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 independently selected R^7 substituents;

Z^1 is N or CR^{8a};

Z^2 is N or CR^{8b};

Z^3 is N or CR^{8c};

R^1, R^2, R^{8a}, R^{8b} and R^{8c} are each independently selected from H, C, alkyl, C_{3-4} 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 selected from H and 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^1, R^2, R^{8a}, R^{8b} and R^{8c} are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN and C_{1-4} alkoxy;

R^9 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 C_{1-4} alkyl, cyclopropyl, C_{2-4} alkynyl and C_{1-4} alkoxy of R^9 are each optionally substituted with 1 or 2 substituents selected from halo, OH, CN and OCH_3 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 substituents;

R^3, R^4, R^5, R^6 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^3, R^4, R^5, R^6 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, with the proviso that at least one of R^3, R^4, R^5 and R^6 is other than H;

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

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, $C(O)R^g$, $C(O)NR^gR^g$, $C(O)OR^g$, $OC(O)R^g$, $OC(O)NR^gR^g$, 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^{11} substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halo, CN, $NHOR^o$, 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^e, $NHOR^i$, $C(O)R^i$, $C(O)NR^iR^i$, $C(O)OR^i$, $OC(O)R^i$, $OC(O)NR^iR^i$, 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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each further optionally substituted by 1, 2, or 3 IV 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

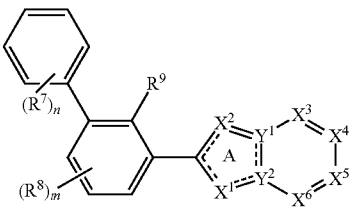
each R^e, R^i, R^k, R^o or R^p is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, C_{2-4} alkenyl, 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} haloalkoxy, C_{1-6} alkylthio, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, C_{3-6} cycloalkyl, NHR^{12}, $NR^{12}R^{12}$, 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^{12} is independently C_{1-6} alkyl; and

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

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

(I)



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

one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;

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;

X^5 is N or CR^5;

X^6 is N or CR^6;

R^1, R^2 and R^8 are each independently selected from H, C_{1-4} alkyl, C_{3-4} 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 selected from H and 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^1, R^2 or R^8 are each optionally substituted with 1 or 2 substituents independently selected from halo, OH, CN and C_{1-4} alkoxy;

R^9 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;

R^3, R^4, R^5, R^6 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^3, R^4, R^5, R^6 and R^7 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, with the proviso that at least one of R^3, R^4, R^5 and R^6 is other than H;

or two adjacent R^7 substituents on the phenyl ring, taken together with the carbon atoms to which they are attached, form a fused phenyl ring, a fused 5-, 6- or 7-membered heterocycloalkyl ring, a fused 5- or 6-membered heteroaryl ring or a fused C_{5-6} cycloalkyl ring, wherein the fused 5-, 6- or 7-membered heterocycloalkyl ring and fused 5- or 6-membered heteroaryl ring each have 1-4 heteroatoms as ring members selected from N, O and S and wherein the fused phenyl ring, fused 5-, 6- or 7-membered heterocycloalkyl ring, fused 5- or 6-membered heteroaryl ring and fused C_{5-6} cycloalkyl ring are each optionally substituted with 1 or 2 independently selected R^q 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-, (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, $NHOR^o$, 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^1, 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-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each further optionally substituted by 1, 2, or 3 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^{12}, $NR^{12}R^{12}$, 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 4-6 membered heterocycloalkyl and each R^{12} is independently C_{1-6} alkyl;

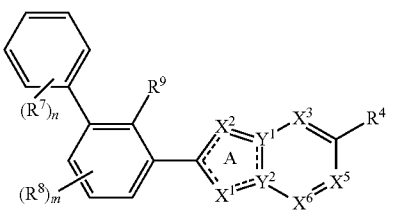
----- is a single bond or a double bond to maintain ring A being aromatic;

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

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

4. The compound of any one of claims **1-3**, having Formula (II):

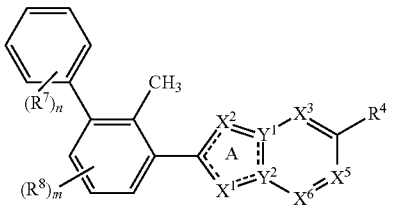
(II)



wherein R^4 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^4 are each optionally substituted with 1, 2, 3, or 4 R^b substituents, or a pharmaceutically acceptable salt or a stereoisomer thereof.

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

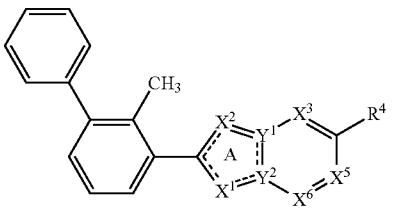
(III)



or a pharmaceutically acceptable salt or a stereoisomer thereof.

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

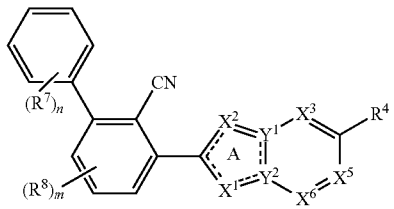
(IV)



or a pharmaceutically acceptable salt or a stereoisomer thereof.

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

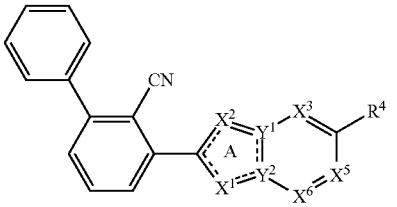
(V)



or a pharmaceutically acceptable salt or a stereoisomer thereof.

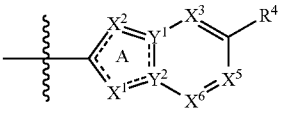
8. The compound of any one of claims **1-4**, having Formula (VI):

(VI)

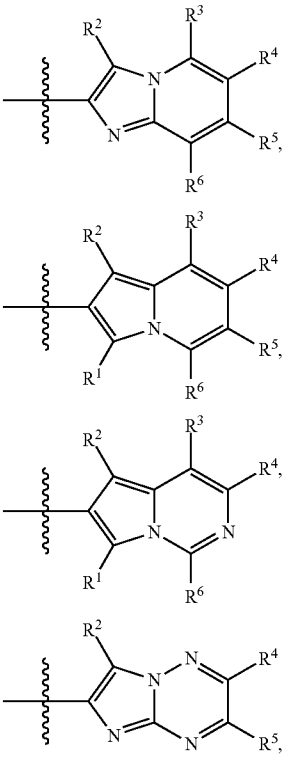


or a pharmaceutically acceptable salt or a stereoisomer thereof.

9. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the moiety:



is selected from:



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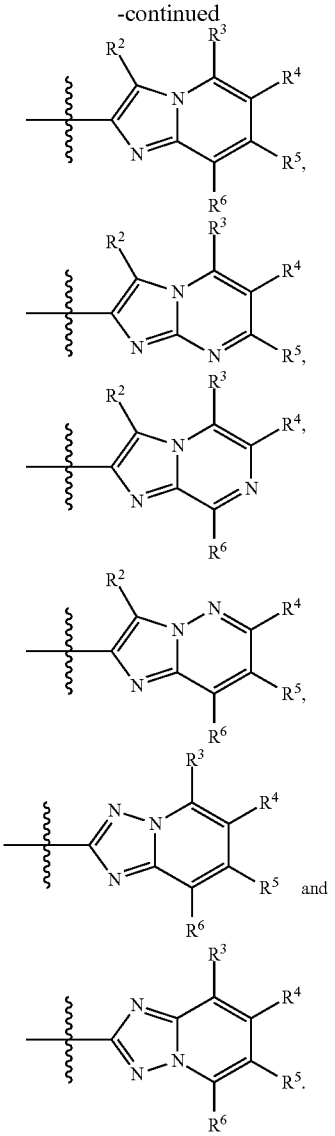

and

10. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^1, R^2, R^3 and R^5 are each H.

11. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N, X^2 is CH, X^3, X^5 and X^6 are each CH, Y^1 is N and Y^2 is C.

12. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is CH, X^2 is CH, X^3, X^5 and X^6 are each CH, Y^1 is C and Y^2 is N.

13. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is CH, X^2 is CH, X^3 and X^6 are each CH, X^5 is N, Y^1 is C and Y^2 is N.

14. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N, X^2 is CH, X^3 and X^6 are each N, X^5 is CH, Y^1 is N and Y^2 is C.

15. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N, X^2 is CH, X^3 and X^5 are each CH, X^6 is N, Y^1 is N and Y^2 is C.

16. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N, X^2 is CH, X^3 and X^6 are each CH, X^5 is N, Y^1 is N and Y^2 is C.

17. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N, X^2 is CH, X^5 and X^6 are each CH, X^3 is N, Y^1 is N and Y^2 is C.

18. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 and X^2 are each N, X^3, X^5 and X^6 are each CH, Y^1 is C and Y^2 is N.

19. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 and X^2 are each N, X^3 is CH, X^5 is N, X^6 is CR^6, Y^1 is C and Y^2 is N.

20. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N, X^2 is CH, X^3 and X^5 are each CH, X^6 is CR^6, Y^1 is N and Y^2 is C.

21. The compound of any one of claims **1-8**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 and X^2 are each N, X^3 and X^5 are each CH, X^6 is CR^6, Y^1 is N and Y^2 is C.

22. The compound of any one of claims **1-21**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^4 is $—CH_2—R^b$.

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

24. The compound of any of claims **1-23**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^4 is 2-hydroxyethylaminomethyl, 2-hydroxyethyl(methyl) aminomethyl, 2-carboxypiperidin-1-yl methyl, (cyanomethyl)aminomethyl, (S)-2-carboxypiperidin-1-ylmethyl or (R)-2-carboxypiperidin-1-ylmethyl.

25. The compound of claim **1**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the compound is selected from:

2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl]methyl}amino)ethanol;

2-({[2-(2-methylbiphenyl-3-yl)indolizin-7-yl] methyl}amino)ethanol;

(2 S)-1-{[2-(2-methylbiphenyl-3-yl)indolizin-7-yl] methyl}piperidine-2-carboxylic acid;

(2S)-1-{[6-(2-methylbiphenyl-3-yl)pyrrolo[1,2-c]pyrimidin-3-yl]methyl}piperidine-2-carboxylic acid;

2-((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methylamino)ethanol;

2-((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methylamino)acetonitrile;

2-((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methylamino)acetamide;

2-(methyl((6-(2-methylbiphenyl-3-yl)imidazo[1,2-b][1,2,4]triazin-2-yl)methyl)amino)ethanol;

2-((8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a] pyridin-6-yl)methylamino)ethanol;

(S)-1-((8-methyl-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl)methyl)piperidine-2-carboxylic acid;

2-((8-chloro-2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyridin-6-yl)methylamino)ethanol;

2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrimidin-6-yl]methyl}amino)ethanol;

2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-a]pyrazin-6-yl]methyl}amino)ethanol;

(S)-1-((2-(2-methylbiphenyl-3-yl)imidazo[1,2-b]pyridazin-6-yl)methyl)piperidine-2-carboxylic acid;

2-({[2-(2-methylbiphenyl-3-yl)imidazo[1,2-b]pyridazin-6-yl]methyl}amino)ethanol;

2-({[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]methyl}amino)ethanol;

(2S)-1-{[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]methyl}piperidine-2-carboxylic acid;

2-({[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}amino)ethanol;

(2S)-1-{[2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}piperidine-2-carboxylic acid; and

2-({[5-methyl-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-c]pyrimidin-7-yl]methyl}amino)ethanol.

26. The compound of claim **1**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the compound is selected from:

2-({[8-chloro-2-(2-methylbiphenyl-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}amino)ethanol;

2-({[8-[(2-methoxyethyl)amino]-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-6-yl]methyl}amino)ethanol;

4-[6-{[(2-hydroxyethyl)amino]methyl}-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-8-yl]butanenitrile;

[6-{[(2-hydroxyethyl)amino]methyl}-2-(2-methylbiphenyl-3-yl)[1,2,4]triazolo[1,5-a]pyridin-8-yl]acetonitrile;

2-(8-chloro-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile;

2-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile; and

2-(8-(cyano methyl)-6-{[(2-hydroxyethyl)amino]methyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)-6-(2,3-dihydro-1,4-benzodioxin-6-yl)benzonitrile.

27. A pharmaceutical composition comprising a compound of any one of claims **1**-**26**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

28. A method of inhibiting PD-1/PD-L1 interaction, said method comprising administering to an individual a compound of any one of claims **1**-**26**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

29. A method of treating a disease or disorder associated with inhibition of PD-1/PD-L1 interaction, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims **1**-**26**, or a pharmaceutically acceptable salt or a stereoisomer thereof, or a composition of claim **27**.

30. The method of claim **29**, wherein the disease or disorder is a viral infection or cancer.

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