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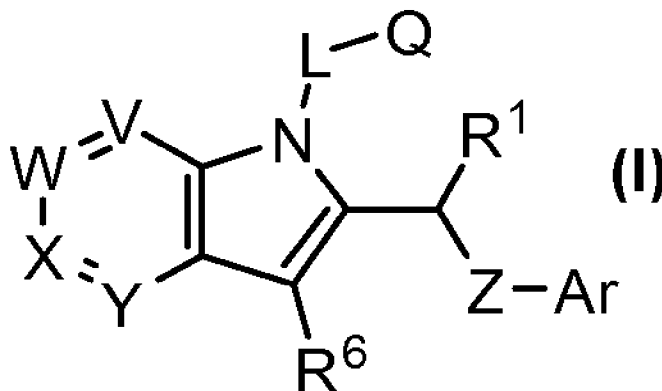
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(54) Title: FUSED PYRROLE DERIVATIVES AS PI3K INHIBITORS



(57) Abstract: The present invention provides fused pyrrole derivatives of Formula (I) wherein V, W, X, Y, L, Q, Ar, Z, R<sup>1</sup> and R<sup>6</sup> are defined herein, that modulate the activity of phosphoinositide 3-kinases (PI3Ks) and are useful in the treatment of diseases related to the activity of PI3Ks including, for example, inflammatory disorders, immune-based disorders, cancer, and other diseases.

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## FUSED PYRROLE DERIVATIVES AS PI3K INHIBITORS

This application claims the benefit of priority of U.S. Provisional Application No. 5 61/356,976, filed June 21, 2010, which is incorporated herein by reference in its entirety.

### TECHNICAL FIELD

The present invention provides fused pyrrole derivatives that modulate the activity of phosphoinositide 3-kinases (PI3Ks) and are useful in the treatment of 10 diseases related to the activity of PI3Ks including, for example, inflammatory disorders, immune-based disorders, cancer, and other diseases.

### BACKGROUND

The phosphoinositide 3-kinases (PI3Ks) belong to a large family of lipid signaling kinases that phosphorylate phosphoinositides at the D3 position of the 15 inositol ring (Cantley, Science, 2002, 296(5573):1655-7). PI3Ks are divided into three classes (class I, II, and III) according to their structure, regulation and substrate specificity. Class I PI3Ks, which include PI3K $\alpha$ , PI3K $\beta$ , PI3K $\gamma$ , and PI3K $\delta$ , are a family of dual specificity lipid and protein kinases that catalyze the phosphorylation of phosphatidylinosito-4,5-bisphosphate (PIP<sub>2</sub>) giving rise to phosphatidylinosito- 20 3,4,5-trisphosphate (PIP<sub>3</sub>). PIP<sub>3</sub> functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion and migration. All four class I PI3K isoforms exist as heterodimers composed of a catalytic subunit (p110) and a tightly associated regulatory subunit that controls their expression, activation, and subcellular localization. PI3K $\alpha$ , PI3K $\beta$ , and PI3K $\delta$  associate with a 25 regulatory subunit known as p85 and are activated by growth factors and cytokines through a tyrosine kinase-dependent mechanism (Jimenez, et al., J Biol Chem., 2002, 277(44):41556-62) whereas PI3K $\gamma$  associates with two regulatory subunits (p101 and p84) and its activation is driven by the activation of G-protein-coupled receptors (Brock, et al., J Cell Biol., 2003, 160(1):89-99). PI3K $\alpha$  and PI3K $\beta$  are ubiquitously 30 expressed. In contrast, PI3K $\gamma$  and PI3K $\delta$  are predominantly expressed in leukocytes (Vanhaesebroeck, et al., Trends Biochem Sci., 2005, 30(4):194-204).

The differential tissue distribution of the PI3K isoforms factors in their distinct biological functions. Genetic ablation of either PI3K $\alpha$  or PI3K $\beta$  results in embryonic

lethality, indicating that PI3K $\alpha$  and PI3K $\beta$  have essential and non-redundant functions, at least during development (Vanhaesebroeck, et al., 2005). In contrast, mice which lack PI3K $\gamma$  and PI3K $\delta$  are viable, fertile and have a normal life span although they show an altered immune system. PI3K $\gamma$  deficiency leads to impaired recruitment of macrophages and neutrophils to sites of inflammation as well as impaired T cell activation (Sasaki, et al., Science, 2000, 287(5455):1040-6). PI3K $\delta$ -mutant mice have specific defects in B cell signaling that lead to impaired B cell development and reduced antibody responses after antigen stimulation (Clayton, et al., J Exp Med. 2002, 196(6):753-63; Jou, et al., Mol Cell Biol. 2002, 22(24):8580-91; Okkenhaug, et al., Science, 2002, 297(5583):1031-4).

The phenotypes of the PI3K $\gamma$  and PI3K $\delta$ -mutant mice suggest that these enzymes may play a role in inflammation and other immune-based diseases and this is borne out in preclinical models. PI3K $\gamma$ -mutant mice are largely protected from disease in mouse models of rheumatoid arthritis (RA) and asthma (Camps, et al., Nat Med. 2005, 11(9):936-43; Thomas, et al., Eur J Immunol. 2005, 35(4):1283-91). In addition, treatment of wild-type mice with a selective inhibitor of PI3K $\gamma$  was shown to reduce glomerulonephritis and prolong survival in the MRL-lpr model of systemic lupus nephritis (SLE) and to suppress joint inflammation and damage in models of RA (Barber, et al., Nat Med. 2005, 11(9):933-5; Camps, et al., 2005). Similarly, both PI3K $\delta$ -mutant mice and wild-type mice treated with a selective inhibitor of PI3K $\delta$  have been shown to have attenuated allergic airway inflammation and hyper-responsiveness in a mouse model of asthma (Ali, et al., Nature. 2004, 431(7011):1007-11; Lee, et al., FASEB J. 2006, 20(3):455-65) and to have attenuated disease in a model of RA (Randis, et al., Eur. J. Immunol., 2008, 38(5):1215-24).

In addition to their potential role in inflammatory diseases, all four class I PI3K isoforms may play a role in cancer. The gene encoding p110 $\alpha$  is mutated frequently in common cancers, including breast, prostate, colon and endometrial (Samuels, et al., Science, 2004, 304(5670):554; Samuels, et al., Curr Opin Oncol. 2006, 18(1):77-82). Eighty percent of these mutations are represented by one of three amino acid substitutions in the helical or kinase domains of the enzyme and lead to a significant upregulation of kinase activity resulting in oncogenic transformation in cell culture and in animal models (Kang, et al., Proc Natl Acad Sci U S A. 2005, 102(3):802-7; Bader, et al., Proc Natl Acad Sci U S A. 2006, 103(5):1475-9). No

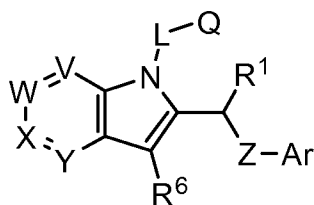
such mutations have been identified in the other PI3K isoforms although there is evidence that they can contribute to the development and progression of malignancies.

5 Consistent overexpression of PI3K $\delta$  is observed in acute myeloblastic leukemia (Sujobert, et al., Blood, 2005, 106(3):1063-6) and inhibitors of PI3K $\delta$  can prevent the growth of leukemic cells (Billottet, et al., Oncogene. 2006, 25(50):6648-59). Elevated expression of PI3K $\gamma$  is seen in chronic myeloid leukemia (Hickey, et al., J Biol Chem. 2006, 281(5):2441-50). Alterations in expression of PI3K $\beta$ ,  
 10 PI3K $\gamma$  and PI3K $\delta$  have also been observed in cancers of the brain, colon and bladder (Benistant, et al., Oncogene, 2000, 19(44):5083-90; Mizoguchi, et al., Brain Pathol. 2004, 14(4):372-7; Knobbe, et al., Neuropathol Appl Neurobiol. 2005, 31(5):486-90). Further, these isoforms have all been shown to be oncogenic in cell culture (Kang, et al., 2006).

15 Thus, new or improved agents which inhibit kinases such as PI3K are continually needed for developing new and more effective pharmaceuticals that are aimed at augmentation or suppression of the immune and inflammatory pathways (such as immunosuppressive agents for organ transplants), as well as agents for the prevention and treatment of autoimmune diseases (*e.g.*, multiple sclerosis, rheumatoid  
 20 arthritis, asthma, type I diabetes, inflammatory bowel disease, Crohn's disease, autoimmune thyroid disorders, Alzheimer's disease, nephritis), diseases involving a hyperactive inflammatory response (*e.g.*, eczema), allergies, lung diseases, cancer (*e.g.*, prostate, breast, leukemia, multiple myeloma), and some immune reactions (*e.g.*, skin rash or contact dermatitis or diarrhea) caused by other therapeutics. The  
 25 compounds, compositions, and methods described herein are directed toward these needs and other ends.

### SUMMARY

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



I

30

or a pharmaceutically acceptable salt thereof; wherein V, W, X, Y, L, Q, R<sup>1</sup>, R<sup>6</sup>, Z, and Ar are defined *infra*.

5 The present invention further provides compositions comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention also provides methods of modulating an activity of a PI3K kinase, comprising contacting the kinase with a compound of the invention, or a  
10 pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating a disease in a patient, wherein the disease is associated with abnormal expression or activity of a PI3K kinase, comprising administering to the patient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

15 The present invention further provides methods of treating an immune-based disease in a patient, comprising administering to the patient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The present invention also provides methods of treating a cancer in a patient, comprising administering to the patient a therapeutically effective amount of a  
20 compound of the invention, or a pharmaceutically acceptable salt thereof.

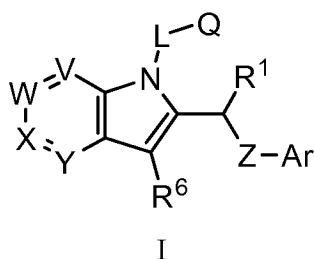
The present invention further provides methods of treating a lung disease in a patient, comprising administering to the patient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

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

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

30 **DETAILED DESCRIPTION**

The present invention provides, *inter alia*, a compound of Formula I:



5 or a pharmaceutically acceptable salt thereof; wherein:

V is CR<sup>2</sup> or N;

W is CR<sup>3</sup> or N;

X is CR<sup>4</sup> or N;

Y is CR<sup>5</sup> or N;

10 provided that -V=W-X=Y- is selected from -CR<sup>2</sup>=CR<sup>3</sup>-CR<sup>4</sup>=CR<sup>5</sup>-,  
-N=CR<sup>3</sup>-CR<sup>4</sup>=CR<sup>5</sup>-, -CR<sup>2</sup>=N-CR<sup>4</sup>=CR<sup>5</sup>-, -CR<sup>2</sup>=CR<sup>3</sup>-N=CR<sup>5</sup>-, and -CR<sup>2</sup>=CR<sup>3</sup>-CR<sup>4</sup>=N-  
;

Z is a bond, O, S, or NR<sup>A</sup>;

L is a bond or C<sub>1-4</sub> alkylene;

15 provided that when L is C<sub>1-4</sub> alkylene, then Z is O, S, or NR<sup>A</sup>;

provided that when Z is a bond, then Ar is attached to Z at a nitrogen atom of

Ar;

provided that when R<sup>6</sup> is bromo or -CO<sub>2</sub>(ethyl), then Z is bond, O, or NR<sup>A</sup>;

Q is C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, or Cy; wherein C<sub>1-6</sub> alkyl, C<sub>2-6</sub>

20 alkenyl, and C<sub>2-6</sub> alkynyl are each optionally substituted by 1, 2, 3, 4, or 5  
independently selected R<sup>C</sup> groups;

Cy is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is  
optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups;

25 each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl,  
CN, NO<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>,  
NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, C(=NR<sup>e</sup>)R<sup>b</sup>, C(=NR<sup>e</sup>)NR<sup>c</sup>R<sup>d</sup>,  
NR<sup>c</sup>C(=NR<sup>e</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>,  
S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>; wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl,  
30 cycloalkyl, heteroaryl, and heterocycloalkyl are each optionally substituted with 1, 2,  
3, 4, or 5 substituents independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, CN, NO<sub>2</sub>, OR<sup>a2</sup>, SR<sup>a2</sup>, C(O)R<sup>b2</sup>, C(O)NR<sup>c2</sup>R<sup>d2</sup>,

$C(O)OR^{a2}$ ,  $OC(O)R^{b2}$ ,  $OC(O)NR^{c2}R^{d2}$ ,  $C(=NR^e)NR^{c2}R^{d2}$ ,  $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$ ,  
 $NR^{c2}R^{d2}$ ,  $NR^{c2}C(O)R^{b2}$ ,  $NR^{c2}C(O)OR^{a2}$ ,  $NR^{c2}C(O)NR^{c2}R^{d2}$ ,  $NR^{c2}S(O)R^{b2}$ ,  
 5  $NR^{c2}S(O)_2R^{b2}$ ,  $NR^{c2}S(O)_2NR^{c2}R^{d2}$ ,  $S(O)R^{b2}$ ,  $S(O)NR^{c2}R^{d2}$ ,  $S(O)_2R^{b2}$ , and  
 $S(O)_2NR^{c2}R^{d2}$ ;

$R^1$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{2-6}$  alkenyl,  
 and  $C_{2-6}$  alkynyl; wherein the  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl are each  
 optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo,  
 10 OH, CN,  $NR^{1a}R^{2b}$ ,  $C_{1-6}$  alkoxy,  $C_{1-6}$  haloalkoxy, thio,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkylsulfinyl,  
 $C_{1-6}$  alkylsulfonyl, carbamyl,  $C_{1-6}$  alkylcarbamyl, di( $C_{1-6}$  alkyl)carbamyl, carboxy,  $C_{1-6}$   
 alkylcarbonyl,  $C_{1-6}$  alkoxy carbonyl,  $C_{1-6}$  alkylcarbonylamino,  $C_{1-6}$  alkylsulfonylamino,  
 aminosulfonyl,  $C_{1-6}$  alkylaminosulfonyl, di( $C_{1-6}$  alkyl)aminosulfonyl,  
 aminosulfonylamino,  $C_{1-6}$  alkylaminosulfonylamino, di( $C_{1-6}$   
 15 alkyl)aminosulfonylamino, aminocarbonylamino,  $C_{1-6}$  alkylaminocarbonylamino, and  
 di( $C_{1-6}$  alkyl)aminocarbonylamino;

each  $R^{1a}$  and  $R^{2b}$  is independently selected from H and  $C_{1-6}$  alkyl;

or any  $R^{1a}$  and  $R^{2b}$  together with the N atom to which they are attached form a  
 4-, 5-, 6-, or 7-membered heterocycloalkyl group, which is optionally substituted with  
 20 1, 2, 3, or 4 substituents independently selected from  $C_{1-6}$  alkyl;

$R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are each independently selected from H, OH,  $NO_2$ , CN,  
 halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-7}$  cycloalkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkoxy,  
 $C_{1-6}$  haloalkoxy, amino,  $C_{1-6}$  alkylamino, di( $C_{1-6}$  alkyl)amino, thio,  $C_{1-6}$  alkylthio,  $C_{1-6}$   
 alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl, carbamyl,  $C_{1-6}$  alkylcarbamyl, di( $C_{1-6}$  alkyl)carbamyl,  
 25 carboxy,  $C_{1-6}$  alkylcarbonyl,  $C_{1-6}$  alkoxy carbonyl,  $C_{1-6}$  alkylcarbonylamino,  $C_{1-6}$   
 alkylsulfonylamino, aminosulfonyl,  $C_{1-6}$  alkylaminosulfonyl, di( $C_{1-6}$   
 alkyl)aminosulfonyl, aminosulfonylamino,  $C_{1-6}$  alkylaminosulfonylamino, di( $C_{1-6}$   
 alkyl)aminosulfonylamino, aminocarbonylamino,  $C_{1-6}$  alkylaminocarbonylamino, and  
 di( $C_{1-6}$  alkyl)aminocarbonylamino;

30 Ar is bicyclic azaheteroaryl, substituted with n independently selected  $R^D$   
 groups; wherein n is 0, 1, 2, 3, 4, or 5;

each  $R^D$  is independently selected from  $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$ , halo,  $C_{1-6}$  alkyl,  $C_{2-6}$   
 alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halosulfonyl, CN,  $NO_2$ ,  $OR^{a1}$ ,  $SR^{a1}$ ,  $C(O)R^{b1}$ ,  
 $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $OC(O)R^{b1}$ ,  $OC(O)NR^{c1}R^{d1}$ ,  $C(=NR^e)NR^{c1}R^{d1}$ ,  
 35  $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$ ,  $NR^{c1}R^{d1}$ ,  $NR^{c1}C(O)R^{b1}$ ,  $NR^{c1}C(O)OR^{a1}$ ,  $NR^{c1}C(O)NR^{c1}R^{d1}$ ,

$\text{NR}^{\text{cl}}\text{S}(\text{O})\text{R}^{\text{bl}}$ ,  $\text{NR}^{\text{cl}}\text{S}(\text{O})_2\text{R}^{\text{bl}}$ ,  $\text{NR}^{\text{cl}}\text{S}(\text{O})_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$ ,  $\text{S}(\text{O})\text{R}^{\text{bl}}$ ,  $\text{S}(\text{O})\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$ ,  $\text{S}(\text{O})_2\text{R}^{\text{bl}}$ ,  
and  $\text{S}(\text{O})_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$ ;

5  $\text{R}^{\text{A}}$  is selected from H,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl, and  $\text{C}_{2-6}$  alkynyl;

each  $\text{Cy}^1$  is, independently, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl,  
each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from  
OH,  $\text{NO}_2$ , CN, halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{1-6}$  haloalkyl,  $\text{C}_{1-6}$  alkoxy,  
 $\text{C}_{1-6}$  haloalkoxy, amino,  $\text{C}_{1-6}$  alkylamino, di( $\text{C}_{1-6}$  alkyl)amino, thio,  $\text{C}_{1-6}$  alkylthio,  $\text{C}_{1-6}$   
10 alkylsulfinyl,  $\text{C}_{1-6}$  alkylsulfonyl, carbamyl,  $\text{C}_{1-6}$  alkylcarbamyl, di( $\text{C}_{1-6}$  alkyl)carbamyl,  
carboxy,  $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy carbonyl,  $\text{C}_{1-6}$  alkylcarbonylamino,  $\text{C}_{1-6}$   
alkylsulfonylamino, aminosulfonyl,  $\text{C}_{1-6}$  alkylaminosulfonyl, di( $\text{C}_{1-6}$   
alkyl)aminosulfonyl, aminosulfonylamino,  $\text{C}_{1-6}$  alkylaminosulfonylamino, di( $\text{C}_{1-6}$   
alkyl)aminosulfonylamino, aminocarbonylamino,  $\text{C}_{1-6}$  alkylaminocarbonylamino, and  
15 di( $\text{C}_{1-6}$  alkyl)aminocarbonylamino;

each  $\text{R}^{\text{a}}$ ,  $\text{R}^{\text{c}}$ , and  $\text{R}^{\text{d}}$  is independently selected from H,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  
 $\text{C}_{2-6}$  alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
cycloalkylalkyl, and heterocycloalkylalkyl, wherein the  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$   
alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
20 cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5  
substituents independently selected from OH,  $\text{NO}_2$ , CN, halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  
 $\text{C}_{2-6}$  alkynyl,  $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{1-6}$  haloalkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  haloalkoxy, amino,  $\text{C}_{1-6}$   
alkylamino, di( $\text{C}_{1-6}$  alkyl)amino, thio,  $\text{C}_{1-6}$  alkylthio,  $\text{C}_{1-6}$  alkylsulfinyl,  $\text{C}_{1-6}$   
alkylsulfonyl, carbamyl,  $\text{C}_{1-6}$  alkylcarbamyl, di( $\text{C}_{1-6}$  alkyl)carbamyl, carboxy,  $\text{C}_{1-6}$   
25 alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy carbonyl,  $\text{C}_{1-6}$  alkylcarbonylamino,  $\text{C}_{1-6}$  alkylsulfonylamino,  
aminosulfonyl,  $\text{C}_{1-6}$  alkylaminosulfonyl, di( $\text{C}_{1-6}$  alkyl)aminosulfonyl,  
aminosulfonylamino,  $\text{C}_{1-6}$  alkylaminosulfonylamino, di( $\text{C}_{1-6}$   
alkyl)aminosulfonylamino, aminocarbonylamino,  $\text{C}_{1-6}$  alkylaminocarbonylamino, and  
di( $\text{C}_{1-6}$  alkyl)aminocarbonylamino;

30 each  $\text{R}^{\text{b}}$  is independently selected from  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  
aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
cycloalkylalkyl, and heterocycloalkylalkyl, wherein the  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$   
alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5  
35 substituents independently selected from OH,  $\text{NO}_2$ , CN, halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  
 $\text{C}_{2-6}$  alkynyl,  $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{1-6}$  haloalkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  haloalkoxy, amino,  $\text{C}_{1-6}$



alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

10 or any R<sup>c</sup> and R<sup>d</sup> together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

20 each R<sup>e</sup> and R<sup>g</sup> is independently selected from H, C<sub>1-6</sub> alkyl, and CN;  
each R<sup>al</sup>, R<sup>cl</sup>, and R<sup>dl</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

35

each R<sup>b1</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

or any R<sup>c1</sup> and R<sup>d1</sup> together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>a2</sup>, R<sup>c2</sup>, and R<sup>d2</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub>

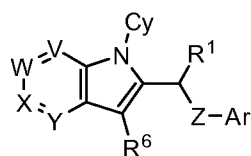
alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub>  
 alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub>  
 5 alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and  
 di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>b2</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl,  
 aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
 cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
 10 alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
 cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5  
 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,  
 C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub>  
 alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub>  
 15 alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub>  
 alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino,  
 aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl,  
 aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub>  
 alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and  
 20 di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

or any R<sup>c2</sup> and R<sup>d2</sup> together with the N atom to which they are attached form a  
 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each  
 optionally substituted with 1, 2, or 3 substituents independently selected from OH,  
 NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl,  
 25 C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub>  
 alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub>  
 alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub>  
 alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl,  
 di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino,  
 30 di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub>  
 alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino; and

r is 0 or 1.

In some embodiments, the compound is a compound of Formula Ia:



Ia

5 or a pharmaceutically acceptable salt thereof; wherein:

V is CR<sup>2</sup> or N;

W is CR<sup>3</sup> or N;

X is CR<sup>4</sup> or N;

Y is CR<sup>5</sup> or N;

10 provided that -V=W-X=Y- is selected from -CR<sup>2</sup>=CR<sup>3</sup>-CR<sup>4</sup>=CR<sup>5</sup>-,  
-N=CR<sup>3</sup>-CR<sup>4</sup>=CR<sup>5</sup>-, -CR<sup>2</sup>=N-CR<sup>4</sup>=CR<sup>5</sup>-, -CR<sup>2</sup>=CR<sup>3</sup>-N=CR<sup>5</sup>-, and -CR<sup>2</sup>=CR<sup>3</sup>-CR<sup>4</sup>=N-  
;

Z is a O, S, or NR<sup>A</sup>;

provided that when R<sup>6</sup> is bromo or -CO<sub>2</sub>(ethyl), then Z is bond, O, or NR<sup>A</sup>;

15 Cy is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is  
optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups;

each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl,  
CN, NO<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>,  
20 NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, C(=NR<sup>e</sup>)R<sup>b</sup>, C(=NR<sup>e</sup>)NR<sup>c</sup>R<sup>d</sup>,  
NR<sup>c</sup>C(=NR<sup>e</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>,  
S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>; wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl,  
cycloalkyl, heteroaryl, and heterocycloalkyl are each optionally substituted with 1, 2,  
3, 4, or 5 substituents independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
25 alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, CN, NO<sub>2</sub>, OR<sup>a2</sup>, SR<sup>a2</sup>, C(O)R<sup>b2</sup>, C(O)NR<sup>c2</sup>R<sup>d2</sup>,  
C(O)OR<sup>a2</sup>, OC(O)R<sup>b2</sup>, OC(O)NR<sup>c2</sup>R<sup>d2</sup>, C(=NR<sup>e2</sup>)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>C(=NR<sup>e2</sup>)NR<sup>c2</sup>R<sup>d2</sup>,  
NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>C(O)R<sup>b2</sup>, NR<sup>c2</sup>C(O)OR<sup>a2</sup>, NR<sup>c2</sup>C(O)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>S(O)R<sup>b2</sup>,  
NR<sup>c2</sup>S(O)<sub>2</sub>R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>NR<sup>c2</sup>R<sup>d2</sup>, S(O)R<sup>b2</sup>, S(O)NR<sup>c2</sup>R<sup>d2</sup>, S(O)<sub>2</sub>R<sup>b2</sup>, and  
S(O)<sub>2</sub>NR<sup>c2</sup>R<sup>d2</sup>;

30 R<sup>1</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl,  
and C<sub>2-6</sub> alkynyl; wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, and C<sub>2-6</sub> alkynyl are each  
optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo,  
OH, CN, NR<sup>1a</sup>R<sup>2b</sup>, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl,

C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, 5 aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>1a</sup> and R<sup>2b</sup> is independently selected from H and C<sub>1-6</sub> alkyl;

10 or any R<sup>1a</sup> and R<sup>2b</sup> together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group, which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from C<sub>1-6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are each independently selected from H, OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, 15 C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and 20 di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

Ar is bicyclic azaheteroaryl, substituted with n independently selected R<sup>D</sup> groups; wherein n is 0, 1, 2, 3, 4, or 5;

each R<sup>D</sup> is independently selected from -(C<sub>1-4</sub> alkyl)<sub>r</sub>-Cy<sup>1</sup>, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> 25 alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halosulfonyl, CN, NO<sub>2</sub>, OR<sup>al</sup>, SR<sup>al</sup>, C(O)R<sup>bl</sup>, C(O)NR<sup>cl</sup>R<sup>dl</sup>, C(O)OR<sup>al</sup>, OC(O)R<sup>bl</sup>, OC(O)NR<sup>cl</sup>R<sup>dl</sup>, C(=NR<sup>e</sup>)NR<sup>cl</sup>R<sup>dl</sup>, NR<sup>cl</sup>C(=NR<sup>e</sup>)NR<sup>cl</sup>R<sup>dl</sup>, NR<sup>cl</sup>R<sup>dl</sup>, NR<sup>cl</sup>C(O)R<sup>bl</sup>, NR<sup>cl</sup>C(O)OR<sup>al</sup>, NR<sup>cl</sup>C(O)NR<sup>cl</sup>R<sup>dl</sup>, NR<sup>cl</sup>S(O)R<sup>bl</sup>, NR<sup>cl</sup>S(O)<sub>2</sub>R<sup>bl</sup>, NR<sup>cl</sup>S(O)<sub>2</sub>NR<sup>cl</sup>R<sup>dl</sup>, S(O)R<sup>bl</sup>, S(O)NR<sup>cl</sup>R<sup>dl</sup>, S(O)<sub>2</sub>R<sup>bl</sup>, and S(O)<sub>2</sub>NR<sup>cl</sup>R<sup>dl</sup>;

30 R<sup>A</sup> is selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, and C<sub>2-6</sub> alkynyl;

each Cy<sup>1</sup> is, independently, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> 35 alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub>

alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub>  
alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub>  
5 alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and  
di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>a</sup>, R<sup>c</sup>, and R<sup>d</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,  
C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
10 alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5  
substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,  
C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub>  
alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub>  
15 alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub>  
alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino,  
aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl,  
aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub>  
alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and  
20 di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>b</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl,  
aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
25 cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5  
substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,  
C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub>  
alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub>  
alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub>  
30 alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino,  
aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl,  
aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub>  
alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and  
di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

35 or any R<sup>c</sup> and R<sup>d</sup> together with the N atom to which they are attached form a  
4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each

optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>c</sup> and R<sup>s</sup> is independently selected from H, C<sub>1-6</sub> alkyl, and CN;

each R<sup>al</sup>, R<sup>cl</sup>, and R<sup>dl</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>bl</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-</sub>

<sub>6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub>  
 alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino,  
 5 C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;  
 or any R<sup>c1</sup> and R<sup>d1</sup> together with the N atom to which they are attached form a  
 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each  
 optionally substituted with 1, 2, or 3 substituents independently selected from OH,  
 NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub>  
 10 haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub>  
 alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl,  
 carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub>  
 alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub>  
 alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub>  
 15 alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and  
 di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>a2</sup>, R<sup>c2</sup>, and R<sup>d2</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub>  
 alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl,  
 heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub>  
 20 <sub>6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl,  
 heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted  
 with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub>  
 alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub>  
 haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub>  
 25 alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl,  
 carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub>  
 alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub>  
 alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub>  
 alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and  
 30 di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>b2</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl,  
 aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
 cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
 alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,  
 35 cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5  
 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,



C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

or any R<sup>c2</sup> and R<sup>d2</sup> together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino; and

r is 0 or 1.

In one embodiment of the preceding embodiment, when R<sup>6</sup> is bromo or -CO<sub>2</sub>(ethyl), then Z is O or NR<sup>A</sup>.

In some embodiments, Z is NR<sup>A</sup>.

In some embodiments, Cy is aryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups. In some embodiments, Cy is heterocycloalkyl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups. In some embodiments, Cy is monocyclic heterocycloalkyl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups. In some embodiments, Cy is heteroaryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups. In some embodiments, Cy is monocyclic heteroaryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups. In some embodiments, Cy is a phenyl ring, which is optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups.

In some embodiments, each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, CN, NO<sub>2</sub>, OR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>,

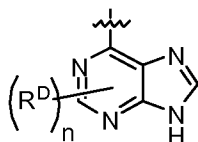
$C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,

$NR^cC(O)NR^cR^d$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein the  $C_{1-6}$

5 alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy,  $C_{1-6}$  alkoxy, and  $C_{1-6}$  haloalkoxy. In some embodiments, each  $R^C$  is independently halo.

In some embodiments, Ar is a purine ring, substituted with n independently selected  $R^D$  groups; wherein n is 0, 1, or 2.

10 In some embodiments, Ar is a moiety of formula:



wherein n is 0 or 1.

In some embodiments, n is 0.

In some embodiments, each  $R^D$  is, independently,  $NR^{c1}R^{d1}$ . In some  
15 embodiments, each  $R^D$  is independently selected from amino,  $C_{1-6}$  alkylamino, and di( $C_{1-6}$ -alkyl)amino.

In some embodiments,  $R^1$  is selected from  $C_{1-6}$  alkyl. In some embodiments,  $R^1$  is methyl.

In some embodiments,  $R^A$  is H.

20 In some embodiments,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are independently selected from H, CN, halo,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkoxy, and  $C_{1-6}$  haloalkoxy. In some embodiments,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are independently selected from H, CN, halo, and  $C_{1-6}$  alkyl.

In some embodiments,  $R^6$  is H, CN, halo, or  $C_{1-6}$  alkyl. In some embodiments,  
25  $R^6$  is H, F, Cl, CN, or methyl.

In some embodiments, V is  $CR^2$ . In some embodiments, V is N.

In some embodiments, W is  $CR^3$ .

In some embodiments, X is  $CR^4$ .

In some embodiments, Y is  $CR^5$ .

30 In some embodiments:

Z is NH;

Cy is heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected  $R^C$  groups;

each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, CN, NO<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>,  
 5 C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>,  
 NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, C(=NR<sup>e</sup>)R<sup>b</sup>, C(=NR<sup>e</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(=NR<sup>e</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)R<sup>b</sup>,  
 NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>;  
 wherein the C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, and C<sub>1-6</sub> haloalkyl are each  
 optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from  
 10 halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, CN, NO<sub>2</sub>,  
 OR<sup>a2</sup>, SR<sup>a2</sup>, C(O)R<sup>b2</sup>, C(O)NR<sup>c2</sup>R<sup>d2</sup>, C(O)OR<sup>a2</sup>, OC(O)R<sup>b2</sup>, OC(O)NR<sup>c2</sup>R<sup>d2</sup>,  
 C(=NR<sup>e2</sup>)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>C(=NR<sup>e2</sup>)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>C(O)R<sup>b2</sup>, NR<sup>c2</sup>C(O)OR<sup>a2</sup>,  
 NR<sup>c2</sup>C(O)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>S(O)R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>NR<sup>c2</sup>R<sup>d2</sup>, S(O)R<sup>b2</sup>,  
 S(O)NR<sup>c2</sup>R<sup>d2</sup>, S(O)<sub>2</sub>R<sup>b2</sup>, and S(O)<sub>2</sub>NR<sup>c2</sup>R<sup>d2</sup>;

15 Ar is a bicyclic azaheteroaryl group, substituted with n independently selected  
 R<sup>D</sup> groups; wherein n is 0, 1, 2, 3, or 4;

each R<sup>D</sup> is, independently, NR<sup>c1</sup>R<sup>d1</sup>;

R<sup>1</sup> is, independently, C<sub>1-6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are independently selected from H, OH, halo, CN, C<sub>1-6</sub>  
 20 alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub>-  
 alkyl)amino, carboxy, C<sub>1-4</sub> alkylcarbonyl, C<sub>1-4</sub> alkoxy carbonyl, carbamyl, C<sub>1-4</sub>  
 alkylcarbamyl, di(C<sub>1-4</sub>-alkyl)carbamyl, C<sub>1-4</sub> alkylcarbonylamino, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub>  
 alkylsulfanyl, and C<sub>1-4</sub> alkylsulfonyl; and

R<sup>6</sup> is H, CN, halo, or C<sub>1-6</sub> alkyl.

25 In some embodiments:

Z is NH;

Cy is heterocycloalkyl, aryl, or heteroaryl, each of which is optionally  
 substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups;

each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub>  
 30 alkynyl, C<sub>1-6</sub> haloalkyl, CN, NO<sub>2</sub>, OR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>,  
 OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>,  
 S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>; wherein the C<sub>1-6</sub> alkyl is optionally  
 substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy, C<sub>1-6</sub>  
 alkoxy, and C<sub>1-6</sub> haloalkoxy;

35 Ar is a purine ring, substituted with n independently selected R<sup>D</sup> groups;  
 wherein n is 0 or 1;

each  $R^D$  is, independently,  $NR^{c1}R^{d1}$ ;

$R^1$  is  $C_{1-6}$  alkyl;

5  $R^2, R^3, R^4,$  and  $R^5$  are each independently selected from H, halo, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkoxy, and  $C_{1-6}$  haloalkoxy; and

$R^6$  is H, CN, halo, or  $C_{1-6}$  alkyl.

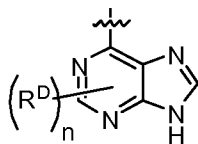
In some embodiments:

Z is NH;

10 Cy is heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected  $R^C$  groups;

each  $R^C$  is independently selected from halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, CN,  $NO_2$ ,  $OR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cC(O)NR^cR^d$ ,  $S(O)R^b$ ,  
 15  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein the  $C_{1-6}$  alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy,  $C_{1-6}$  alkoxy, and  $C_{1-6}$  haloalkoxy;

Ar is a moiety of formula:



20 wherein n is 0 or 1;

each  $R^D$  is, independently,  $NR^{c1}R^{d1}$ ;

$R^1$  is  $C_{1-6}$  alkyl;

$R^2, R^3, R^4,$  and  $R^5$  are each independently selected from H, halo, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkoxy, and  $C_{1-6}$  haloalkoxy; and

25  $R^6$  is H, CN, halo, or  $C_{1-6}$  alkyl.

In some embodiments:

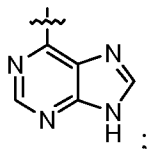
Z is NH;

Cy is heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected  $R^C$  groups;

30 each  $R^C$  is independently selected from halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, CN,  $NO_2$ ,  $OR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cC(O)NR^cR^d$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein the  $C_{1-6}$  alkyl is optionally

substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy, C<sub>1-6</sub> alkoxy, and C<sub>1-6</sub> haloalkoxy;

5 Ar is a moiety of formula:



R<sup>1</sup> is C<sub>1-6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are each independently selected from H, halo, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, and C<sub>1-6</sub> haloalkoxy; and

10 R<sup>6</sup> is H, CN, halo, or C<sub>1-6</sub> alkyl.

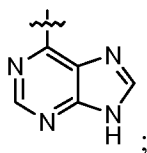
In some embodiments:

Z is NH;

Cy is aryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups;

15 each R<sup>C</sup> is independently selected from halo;

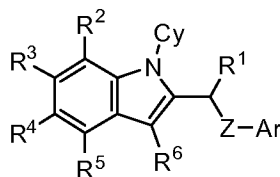
Ar is a moiety of formula:



R<sup>1</sup> is C<sub>1-6</sub> alkyl; and

20 R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are each independently selected from H, halo, CN, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> haloalkyl.

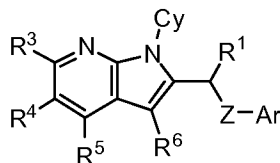
In some embodiments, the compound is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof.

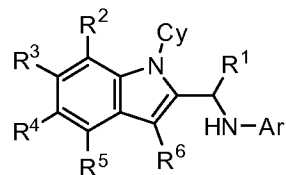
25 In some embodiments, the compound is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof.

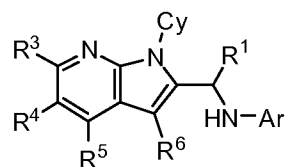
5 In some embodiments, the compound is a compound of Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is a compound of Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is selected from:

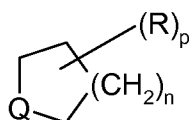
- 15 *N*-{1-[6-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;  
*N*-{1-[4-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;  
*N*-{1-[3-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;  
*N*-{1-[3,4-dichloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;  
*N*-{1-[3-bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;  
20 *N*-{1-[3-chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}-9H-purin-6-amine;  
*N*-(1-(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-9H-purin-6-amine;  
*N*-{1-[1-(3-fluorophenyl)-3-methyl-1H-indol-2-yl]ethyl}-9H-purin-6-amine;  
25 2-(1-(9H-purin-6-ylamino)ethyl)-1-(3-fluorophenyl)-1H-indole-3-carbonitrile;  
and  
*N*-(1-(3-fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-9H-purin-6-amine;  
or a pharmaceutically acceptable salt of any of the aforementioned.

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

At various places in the present specification, divalent linking substituents are described. It is specifically intended that each divalent linking substituent include both  
 10 the forward and backward forms of the linking substituent. For example, -NR(CR'R'')<sub>n</sub>- includes both -NR(CR'R'')<sub>n</sub>- and -(CR'R'')<sub>n</sub>NR-. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups.

The term "n-membered" where n is an integer typically describes the number  
 15 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.

For compounds of the invention in which a variable appears more than once, each variable can be a different moiety independently selected from the group  
 20 defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties independently selected from the group defined for R. In another example, when an optionally multiple substituent is designated in the form:



then it is to be understood that substituent R can occur p number of times on the ring, and R can be a different moiety at each occurrence. It is to be understood that each R  
 30 group may replace any hydrogen atom attached to a ring atom, including one or both of the (CH<sub>2</sub>)<sub>n</sub> hydrogen atoms. Further, in the above example, should the variable Q be defined to include hydrogens, such as when Q is to be CH<sub>2</sub>, NH, etc., any floating substituent such as R in the above example, can replace a hydrogen of the Q variable as well as a hydrogen in any other non-variable component of the ring.

As used herein, the phrase “optionally substituted” means unsubstituted or substituted. As used herein, the term “substituted” means that a hydrogen atom is removed and replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency.

At various places in the present specification, rings are described (e.g., “a piperidine ring”). Unless otherwise specified, these rings can be attached to the rest of the molecule at any ring member as permitted by valency. For example, the term “a pyridine ring” may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

Throughout the definitions, the term “C<sub>n-m</sub>” indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C<sub>1-4</sub>, C<sub>1-6</sub>, and the like.

As used herein, the term “C<sub>n-m</sub> alkyl”, employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbons. 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.

As used herein, the term “alkylene”, employed alone or in combination with other terms, refers to a divalent alkyl linking group. 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.

As used herein, “C<sub>n-m</sub> alkenyl”, employed alone or in combination with other terms, refers to an alkyl group having one or more double carbon-carbon bonds and having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6 or to 2 to 4 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like.

As used herein, “C<sub>n-m</sub> alkynyl” refers to an alkyl group having one or more triple carbon-carbon bonds and having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6 or 2 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkoxy”, employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n



to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like. In some embodiments, the alkyl  
5 group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkylamino” refers to a group of formula -NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkoxy carbonyl” refers to a group of formula  
10 -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkyl carbonyl” refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkyl carbonylamino” refers to a group of  
15 formula -NHC(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkylsulfonylamino” refers to a group of  
formula -NHS(O)<sub>2</sub>-alkyl, wherein the alkyl group has n to m carbon atoms. In some  
20 embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “aminosulfonyl”, employed alone or in combination with other terms, refers to a group of formula -S(O)<sub>2</sub>NH<sub>2</sub>, wherein the alkyl group has n to m carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkylaminosulfonyl” refers to a group of  
25 formula -S(O)<sub>2</sub>NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “di(C<sub>n-m</sub> alkyl)aminosulfonyl” refers to a group of  
formula -S(O)<sub>2</sub>N(alkyl)<sub>2</sub>, wherein each alkyl group independently has n to m carbon  
atoms. In some embodiments, each alkyl group has, independently, 1 to 6 or 1 to 4  
30 carbon atoms.

As used herein, the term “aminosulfonylamino” refers to a group of formula -NHS(O)<sub>2</sub>NH<sub>2</sub>.

As used herein, the term “C<sub>n-m</sub> alkylaminosulfonylamino” refers to a group of  
formula -NHS(O)<sub>2</sub>NH(alkyl), wherein the alkyl group has n to m carbon atoms. In  
35 some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “di(C<sub>n-m</sub> alkyl)aminosulfonylamino” refers to a group of formula -NHS(O)<sub>2</sub>N(alkyl)<sub>2</sub>, wherein each alkyl group independently has n to m  
5 carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “aminocarbonylamino” refers to a group of formula -NHC(O)NH<sub>2</sub>.

As used herein, the term “C<sub>n-m</sub> alkylaminocarbonylamino” refers to a group of  
10 formula -NHC(O)NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “di(C<sub>n-m</sub> alkyl)aminocarbonylamino” refers to a group of formula -NHC(O)N(alkyl)<sub>2</sub>, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6  
15 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkylcarbamyl” refers to a group of formula -C(O)-NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “thio” refers to a group of formula -SH.

As used herein, the term “C<sub>n-m</sub> alkylthio” refers to a group of formula -S-alkyl,  
20 wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkylsulfinyl” refers to a group of formula -S(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments,  
25 the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “C<sub>n-m</sub> alkylsulfonyl” refers to a group of formula -S(O)<sub>2</sub>-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “amino” refers to a group of formula -NH<sub>2</sub>.

As used herein, the term “aryl”, employed alone or in combination with other  
30 terms, refers to a monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) fully aromatic hydrocarbon, such as, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, anthracenyl, phenanthrenyl, and the like. In some embodiments, aryl is C<sub>6-12</sub> aryl. In some embodiments, the aryl group is a naphthalene ring or phenyl ring. In some  
35 embodiments, the aryl group is phenyl.

As used herein, the term “arylalkyl” refers to a group of formula -alkylene-aryl. In some embodiments, arylalkyl is C<sub>6-12</sub> aryl-C<sub>1-3</sub> alkyl. In some embodiments, arylalkyl is benzyl.

As used herein, the term “carbamyl” refers to a group of formula -C(O)NH<sub>2</sub>.

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

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

As used herein, the term “cycloalkyl”, employed alone or in combination with other terms, refers to a non-aromatic cyclic hydrocarbon moiety, which may optionally contain one or more alkenylene groups as part of the ring structure. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized to form carbonyl linkages. In some embodiments, cycloalkyl is C<sub>3-12</sub> cycloalkyl, which is monocyclic or bicyclic. Exemplary cycloalkyl groups include 1,2,3,4-tetrahydro-naphthalene, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, the term “cycloalkylalkyl” refers to a group of formula -alkylene-cycloalkyl. In some embodiments, cycloalkylalkyl is C<sub>3-12</sub> cycloalkyl-C<sub>1-3</sub> alkyl, wherein the cycloalkyl portion is monocyclic or bicyclic.

As used herein, the term “di(C<sub>n-m</sub>-alkyl)amino” refers to a group of formula -N(alkyl)<sub>2</sub>, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “di(C<sub>n-m</sub>-alkyl)carbamyl” refers to a group of formula -C(O)N(alkyl)<sub>2</sub>, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms.

As used herein, “C<sub>n-m</sub> haloalkoxy” refers to a group of formula -O-haloalkyl having n to m carbon atoms. An example haloalkoxy group is OCF<sub>3</sub>. In some

embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

5 As used herein, the term “C<sub>n-m</sub> haloalkyl”, employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms which may be the same or different, where “s” is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the  
10 alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “fluorinated C<sub>n-m</sub> haloalkyl” refers to a C<sub>n-m</sub> haloalkyl wherein the halogen atoms are selected from fluorine. In some embodiments, fluorinated C<sub>n-m</sub> haloalkyl is fluoromethyl, difluoromethyl, or trifluoromethyl. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

15 As used herein, “halosulfanyl” refers to a sulfur group having one or more halogen substituents. Example halosulfanyl groups include pentahalosulfanyl groups such as SF<sub>5</sub>.

As used herein, the term “heteroaryl”, employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings)  
20 fully aromatic hydrocarbon moiety, having one or more heteroatom ring members selected from nitrogen, sulfur and oxygen. In some embodiments, heteroaryl is 5- to 10-membered C<sub>1-9</sub> heteroaryl, which is monocyclic or bicyclic and which has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. When the heteroaryl group contains more than one heteroatom ring member,  
25 the heteroatoms may be the same or different. Example heteroaryl groups include, but are not limited to, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, pyrazole, azolyl, oxazole, thiazole, imidazole, furan, thiophene, quinoline, isoquinoline, indole, benzothiophene, benzofuran, benzisoxazole, imidazo[1,2-b]thiazole, purine, or the like.

30 As used herein, the term “bicyclic azaheteroaryl” refers to a bicyclic fused heteroaryl group having 1, 2, 3, or 4 nitrogen ring members. The bicyclic azaheteroaryl group may optionally have O or S heteroatom ring members in addition to the nitrogen ring members. In some embodiments, the only heteroatom ring members in the bicyclic azaheteroaryl group are nitrogen heteroatoms. In some  
35 embodiments, the bicyclic azaheteroaryl group is C<sub>4-9</sub> bicyclic azaheteroaryl, which has 7 to 10 ring forming atoms independently selected from carbon, nitrogen, sulfur

and oxygen, wherein 1, 2, 3, or 4 of the ring forming atoms are independently selected from nitrogen, sulfur and oxygen provided that at least one ring atom is nitrogen. In  
5 some embodiments, bicyclic azaheteroaryl is a purine ring.

As used herein, the term “heteroarylalkyl” refers to a group of formula –alkylene-heteroaryl. In some embodiments, heteroarylalkyl is  $C_{1-9}$  heteroaryl- $C_{1-3}$  alkyl, wherein the heteroaryl portion is monocyclic or bicyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.

10 As used herein, the term “heterocycloalkyl”, employed alone or in combination with other terms, refers to non-aromatic ring system, which may optionally contain one or more alkenylene or alkynylene groups as part of the ring structure, and which has at least one heteroatom ring member independently selected from nitrogen, sulfur and oxygen. When the heterocycloalkyl groups contains more  
15 than one heteroatom, the heteroatoms may be the same or different. Heterocycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the non-aromatic ring, for example, 1,2,3,4-tetrahydro-quinoline and the like. The carbon  
20 atoms or heteroatoms in the ring(s) of the heterocycloalkyl group can be oxidized to form a carbonyl, or sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized. In some embodiments, heterocycloalkyl is 5- to 10-membered  $C_{2-9}$  heterocycloalkyl, which is monocyclic or bicyclic and which has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.  
25 Examples of heterocycloalkyl groups include 1,2,3,4-tetrahydro-quinoline, azetidine, azepane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, and pyran.

A five-membered ring heteroaryl is a heteroaryl with a ring 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 are thienyl, furyl,  
30 pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring  
35 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.

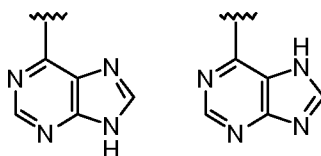
5           As used herein, the term "heterocycloalkylalkyl" refers to a group of formula -alkylene-heterocycloalkyl. In some embodiments, heterocycloalkylalkyl is C<sub>2-9</sub> heterocycloalkyl-C<sub>1-3</sub> alkyl, wherein the heterocycloalkyl portion is monocyclic or bicyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.

10           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  
15 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  
20 mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example 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, for  
25 example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as  $\beta$ -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of  $\alpha$ -methylbenzylamine (*e.g.*, *S* and *R* forms, or  
30 diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

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

Compounds 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, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. For example, purine includes the *9H* and a *7H* tautomeric forms:



Compounds of the invention can include both the *9H* and *7H* tautomeric forms.

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.

The term, “compound,” as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified (e.g., in the case of purine rings, unless otherwise indicated, when the compound name or structure has the *9H* tautomer, it is understood that the *7H* tautomer is also encompassed).

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

In some embodiments, 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, for example, 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 5 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. Methods for isolating compounds and their salts are routine in the art.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope 10 of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, “ambient temperature” and “room temperature,” as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction 15 temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is 20 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 conventional non-toxic salts of the parent compound 25 formed, for example, 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 30 an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (*e.g.*, methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is 35 incorporated herein by reference in its entirety.



*Synthesis*

Compounds of the invention, including salts thereof, can be prepared using  
5 known organic synthesis techniques and can be synthesized according to any of  
numerous possible synthetic routes.

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  
10 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  
15 by the skilled artisan.

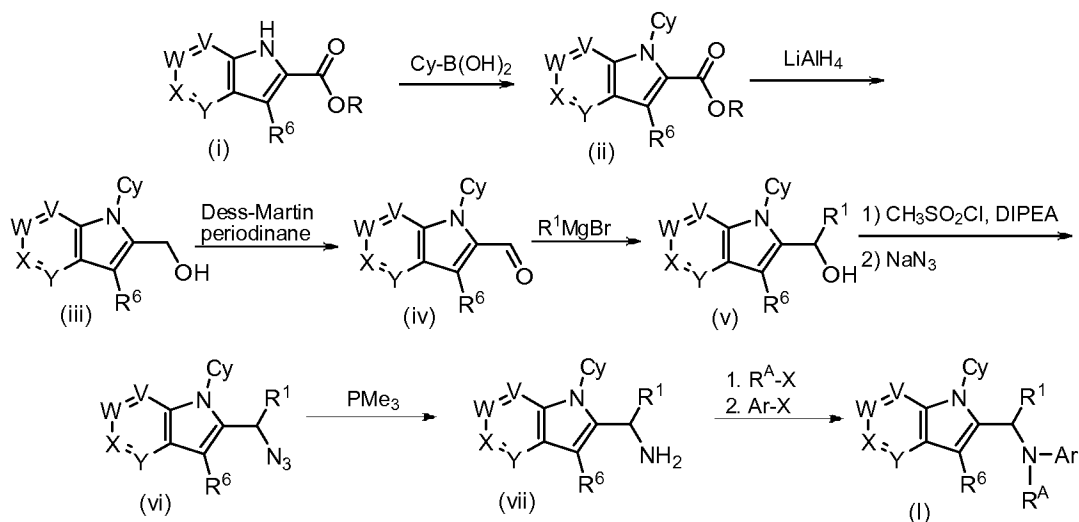
Preparation of compounds of the invention can involve the protection and  
deprotection of various chemical groups. The need for protection and deprotection,  
and the selection of appropriate protecting groups, can be readily determined by one  
skilled in the art. The chemistry of protecting groups can be found, for example, in T.  
20 W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3<sup>rd</sup> Ed., Wiley  
& Sons, Inc., New York (1999), which is incorporated herein by reference in its  
entirety.

Reactions can be monitored according to any suitable method known in the  
art. For example, product formation can be monitored by spectroscopic means, such  
25 as nuclear magnetic resonance spectroscopy (*e.g.*, <sup>1</sup>H or <sup>13</sup>C), infrared spectroscopy,  
spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatographic  
methods such as high performance liquid chromatography (HPLC), liquid  
chromatography-mass spectrometry (LCMS) or thin layer chromatography (TLC).  
Compounds can be purified by those skilled in the art by a variety of methods,  
30 including high performance liquid chromatography (HPLC) ("*Preparative LC-MS  
Purification: Improved Compound Specific Method Optimization*" Karl F. Blom,  
Brian Glass, Richard Sparks, Andrew P. Combs *J. Combi. Chem.* **2004**, 6(6), 874-  
883, which is incorporated herein by reference in its entirety) and normal phase silica  
chromatography.

35 Example synthetic methods for preparing compounds of Formula I, wherein Z  
is NR<sup>A</sup>, are provided in Scheme I. An ester compound of formula (i) (wherein R is

alkyl (e.g., ethyl)) may be reacted with a compound of formula  $\text{Cy-B(OH)}_2$  in the presence of cupric acetate to give a compound of formula (ii). The ester (ii) can then be reduced with an appropriate reducing agent, such as lithium tetrahydroaluminate, to give an alcohol compound of formula (iii). The alcohol (iii) can then be oxidized to an aldehyde compound of formula (iv) using an appropriate oxidizing agent. The aldehyde (iv) may then be reacted with a Grignard reagent of formula  $\text{R}^1\text{-MgBr}$  to give an alcohol of formula (v). The alcohol (v) can be converted to the mesylate and then reacted with sodium azide to give an azide compound of formula (vi). The azide (vi) can then be converted to an amine under appropriate conditions (e.g., treatment with trimethylphosphine) to give an amine of formula (vii). Finally, the amine (vii) can be reacted with an appropriate alkylating agent  $\text{R}^A\text{X}$  (e.g., MeI) and then a heteroaryl halide compound (e.g.,  $\text{Ar-X}^1$ , wherein  $\text{X}^1$  is bromo, iodo, etc.) to give a compound of Formula I. The reaction of amine (vii) with  $\text{R}^A$  can be eliminated to give compounds of Formula I where  $\text{R}^A$  is H.

Scheme I

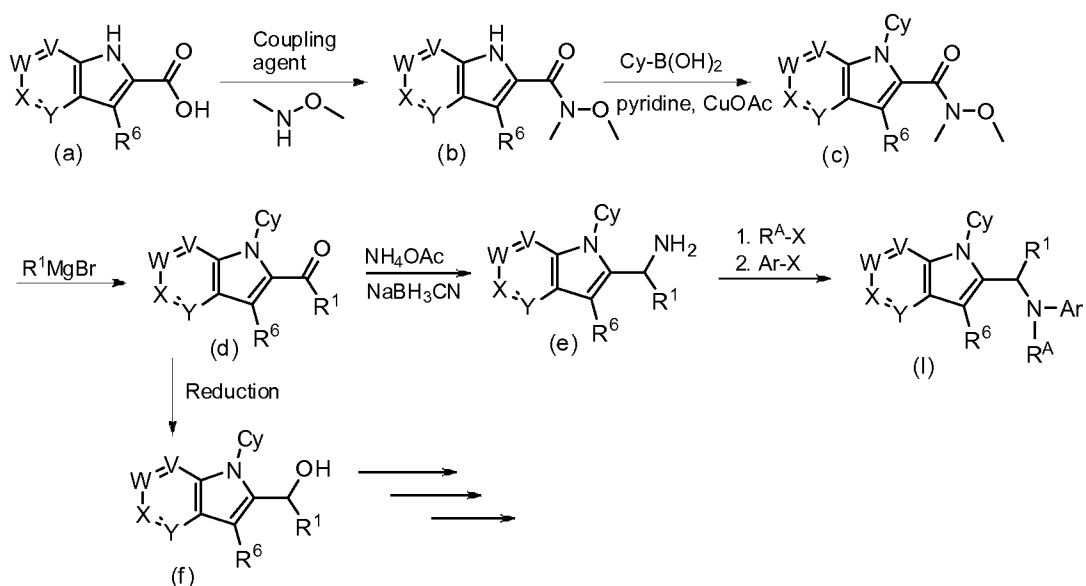


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Compounds of Formula (I), wherein Z is  $\text{NR}^A$ , may also be synthesized as shown in Scheme II. Accordingly, a carboxylic acid of formula (a) can be directly activated with a coupling agent (e.g. HBTU, HATU) and then reacted with *N,O*-dimethylhydroxylamine to give a *N*-methoxy-*N*-methylcarboxamide derivative of formula (b). The carboxamide (ii) may then be reacted with a boronic ester or acid (e.g., a compound of formula  $\text{Cy-B(OH)}_2$ ) in the presence of cupric acetate and

pyridine to give a compound of formula (c). Compound (c) can then be reacted with a Grignard reagent of formula  $R^1$ -MgBr to give a ketone of formula (d). The ketone (d) may be reacted with sodium cyanoborohydride in the presence of ammonium acetate to give the amine of formula (e). The amine (e) can be reacted with an appropriate alkylating agent  $R^A$ X (e.g., MeI) and then a heteroaryl halide compound (e.g., Ar-X) to give a compound of Formula I. The reaction of amine (e) with  $R^A$  can be eliminated to give compounds of Formula I where  $R^A$  is H. Alternatively, the ketone (d) can be reduced to give an alcohol of formula (f) which can be converted to a compound of Formula I by substituting it for the compound of formula (v) in Scheme I.

Scheme II



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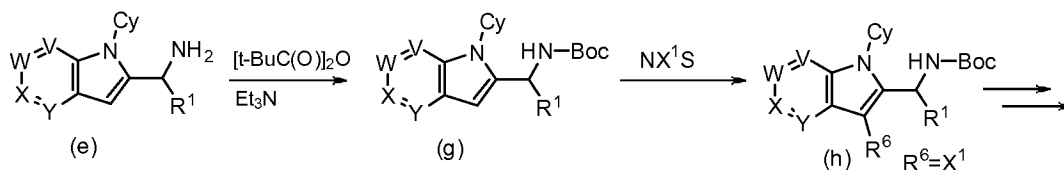
Compounds of Formula I, wherein R<sup>6</sup> is halogen, can also be synthesized as shown in Scheme III. Accordingly, the amine of formula (e) from Scheme II is first protected to give a Boc derivative of formula (g). The Boc derivative (g) can then be reacted with N-halosuccinimide, wherein X<sup>1</sup> is halogen (e.g., bromo, chloro, or iodo) to give a compound of formula (h). The compound of formula (h) can then be deprotected to give an amine compound, which can then be converted to a compound of Formula I using the methods in Scheme I or II (e.g., by substituting the amine

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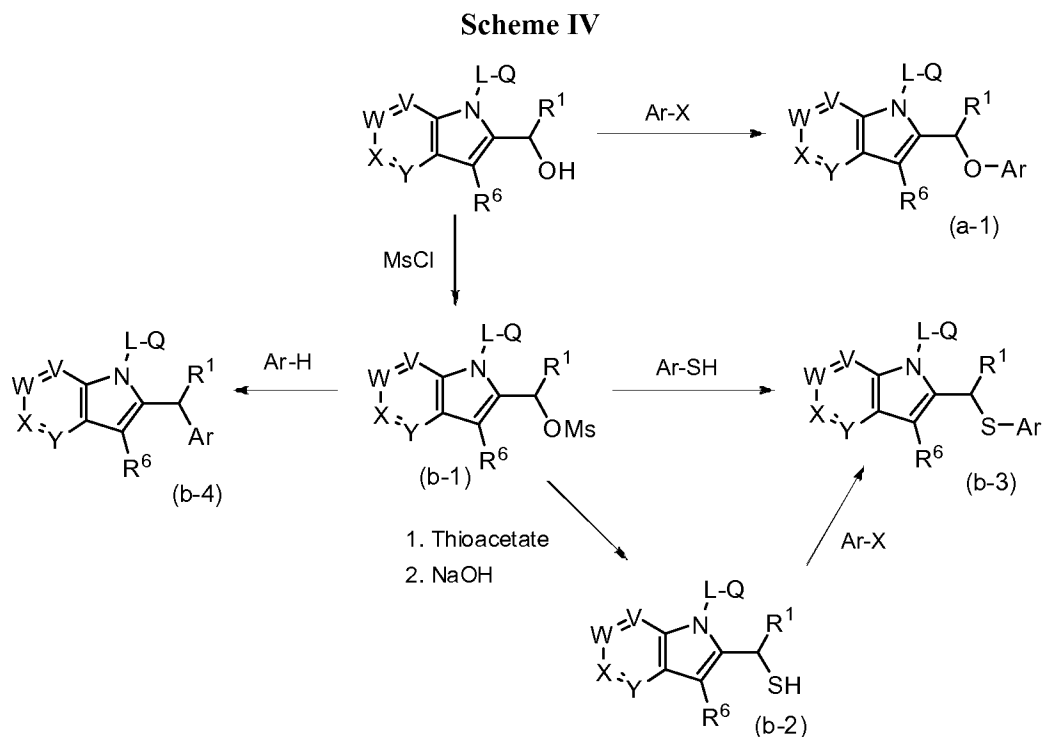
compound for the compound of formula (vii) in Scheme I or the compound of formula (e) in Scheme II).

5

### Scheme III



Alternatively, compounds of Formula I, wherein Z is O, S, or a bond, can be synthesized as shown in Scheme IV. The hydroxyl group of the compound of formula (v) from Scheme I or the compound of formula (f) from Scheme II can be transformed to a thiol group by activation with mesyl chloride to form a mesylate compound of formula (b-1), followed by conversion to the thioacetate and cleavage of the acetate to afford a thiol compound of formula (b-2). The hydroxyl compound (from Scheme I or II) or the thiol compound (b-2) can be reacted with an appropriate heteroaryl halide compound (e.g., Ar-Br) to give a compound of formula (a-1) or (b-3), respectively, with or without a catalyst. Alternatively, the mesylate (b-1) can be reacted with aryl or heteroaryl thiol (e.g., Ar-SH) to give a compound of formula (b-3). The mesylate (b-1) can also be reacted with a heteroaryl compound (e.g., Ar-H, wherein H is attached to a nitrogen atom in Ar) to give a compound of formula (b-4).

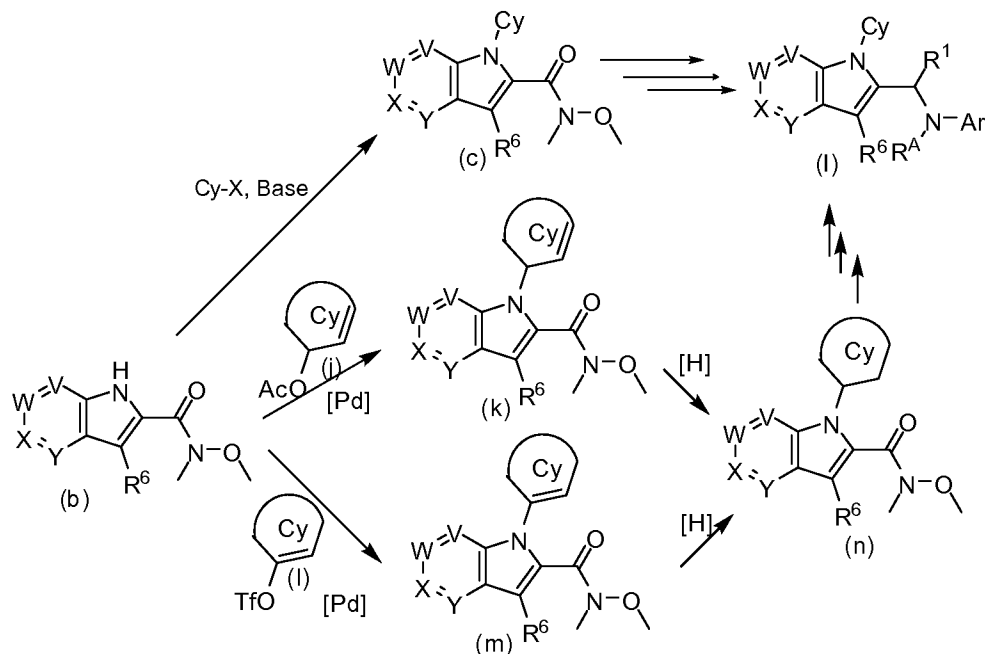


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Compounds of Formula I, wherein Cy is heterocycloalkyl or cycloalkyl, can be synthesized as shown in Scheme V. Appropriate indole compound, for example compound (b) from Scheme II, can be reacted with Cy-X (X is a leaving group such as a bromine or tosylate, mesylate) in the presence of a suitable base (such as sodium hydride, potassium butoxide, or potassium hydroxide) in a suitable solvent (such as DMF or DMSO) to give compound (c). The latter can then be converted to compounds of Formula I, wherein Cy is heterocycloalkyl or cycloalkyl, as shown in Scheme II. Alternatively, compound (c) can be reacted with an allyl carbonate or allyl acetate (i) in the presence of a suitable palladium catalyst such as Pd<sub>2</sub>(dba)<sub>3</sub>, and a suitable ligand such as (1R,2R)-(+)-1,2-diaminocyclohexane-*N,N'*-bis(2-diphenylphosphinobenzoyl) to yield compound (k). Compound (c) can also be treated with vinyl triflate (l) under cross coupling conditions to give compound (m). Compound (k) and (m) can then be hydrogenated to compound (n), which can be further transformed to a compound of Formula I.

20

## Scheme V

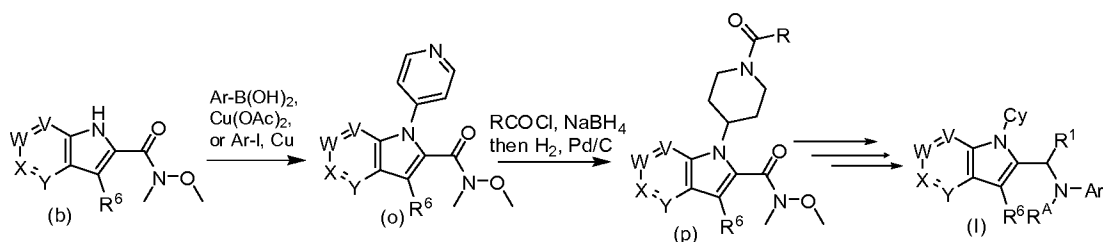


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Compounds with Formulary I, wherein Cy is heterocycloalkyl, can also be prepared by methods analogous to those in Scheme VI. Compound (b) can be converted to compound (o) through coupling with a pyridine boronic acid in the presence of copper(II) acetate or Ulman-type coupling with pyridine iodide in the presence of copper or other modified catalyst. The pyridine ring in compound (o) can then be transformed to a saturated heterocycloalkyl by reaction with an acid chloride or chlorofomate followed by reduction with sodium borohydride and then hydrogenation. The resultant compound (p) can be further modified to provide compounds of Formula I with desired substituted heterocycloalkyl.

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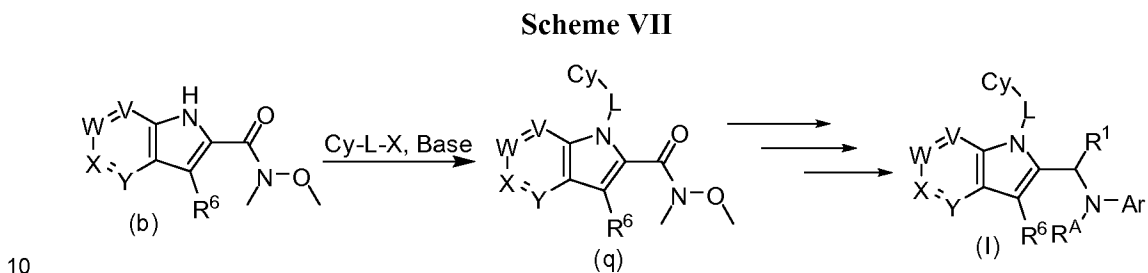
## Scheme VI



Compounds of Formula I, wherein L is alkylene, can be synthesized as shown in Scheme VII. Appropriate indole compound, for example compound (b) from

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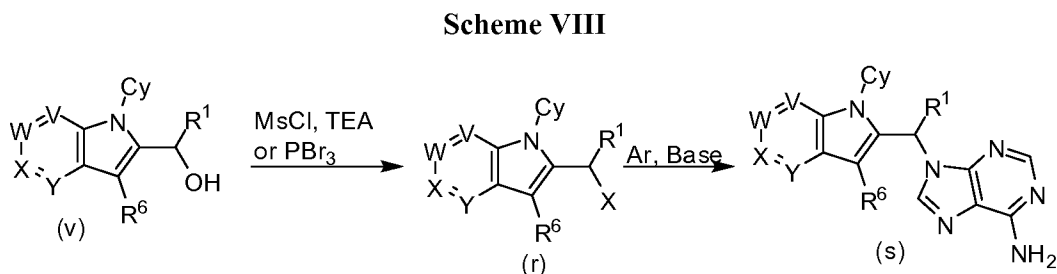
Scheme II, can be reacted with Cy-L-X (X is a leaving group such as a bromine or tosylate, mesylate) in the presence of a suitable base (such as sodium hydride, potassium butoxide, or potassium hydroxide) in a suitable solvent (such as DMF or DMSO) to give compound (q). The latter can then be converted to compounds of Formula I, wherein L is alkylene.



10

Compounds of Formula I, wherein Z is a bond, can be synthesized as shown in Scheme VIII. The hydroxyl group of the compound of formula (v) from Scheme I or the compound of formula (f) from Scheme II can be transformed to a leaving group (e.g. MsO or Br) by activation with mesyl chloride or conversion to halogen directly. The resulting compound (r) can then react with a heteroaryl with a nucleophilic group, for example 6-aminopurine, to give the desired compound of Formula I wherein Z is a bond.

20



## 25 *Methods*

The compounds of the invention can modulate activity of one or more of various kinases including, for example, phosphoinositide 3-kinases (PI3Ks). The term “modulate” is meant to refer to an ability to increase or decrease the activity of one or more members of the PI3K family. Accordingly, the compounds of the

invention can be used in methods of modulating a PI3K by contacting the PI3K with any one or more of the compounds or compositions described herein. In some  
5 embodiments, compounds of the present invention can act as inhibitors of one or more PI3Ks. In further embodiments, the compounds of the invention can be used to modulate activity of a PI3K in an individual in need of modulation of the receptor by administering a modulating amount of a compound of the invention, or a pharmaceutically acceptable salt thereof. In some embodiments, modulating is  
10 inhibiting.

Given that cancer cell growth and survival is impacted by multiple signaling pathways, the present invention is useful for treating disease states characterized by drug resistant kinase mutants. In addition, different kinase inhibitors, exhibiting different preferences in the kinases which they modulate the activities of, may be used  
15 in combination. This approach could prove highly efficient in treating disease states by targeting multiple signaling pathways, reduce the likelihood of drug-resistance arising in a cell, and reduce the toxicity of treatments for disease.

Kinases to which the present compounds bind and/or modulate (e.g., inhibit) include any member of the PI3K family. In some embodiments, the PI3K is PI3K $\alpha$ ,  
20 PI3K $\beta$ , PI3K $\gamma$ , or PI3K $\delta$ . In some embodiments, the PI3K is PI3K $\gamma$  or PI3K $\delta$ . In some embodiments, the PI3K is PI3K $\gamma$ . In some embodiments, the PI3K is PI3K $\delta$ . In some embodiments, the PI3K includes a mutation. A mutation can be a replacement of one amino acid for another, or a deletion of one or more amino acids. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

25 In some embodiments, more than one compound of the invention is used to inhibit the activity of one kinase (e.g., PI3K $\gamma$  or PI3K $\delta$ ).

In some embodiments, more than one compound of the invention is used to inhibit more than one kinase, such as at least two kinases (e.g., PI3K $\gamma$  and PI3K $\delta$ ).

In some embodiments, one or more of the compounds is used in combination  
30 with another kinase inhibitor to inhibit the activity of one kinase (e.g., PI3K $\gamma$  or PI3K $\delta$ ).

In some embodiments, one or more of the compounds is used in combination with another kinase inhibitor to inhibit the activities of more than one kinase (e.g., PI3K $\gamma$  or PI3K $\delta$ ), such as at least two kinases.

35 The compounds of the invention can be selective. By “selective” is meant that the compound binds to or inhibits a kinase with greater affinity or potency,



respectively, compared to at least one other kinase. In some embodiments, the compounds of the invention are selective inhibitors of PI3K $\gamma$  or PI3K $\delta$  over PI3K $\alpha$  and/or PI3K $\beta$ . In some embodiments, the compounds of the invention are selective inhibitors of PI3K $\delta$  (*e.g.*, over PI3K $\alpha$ , PI3K $\beta$  and PI3K $\gamma$ ). In some embodiments, the compounds of the invention are selective inhibitors of PI3K $\gamma$  (*e.g.*, over PI3K $\alpha$ , PI3K $\beta$  and PI3K $\delta$ ). In some embodiments, selectivity can be at least about 2-fold, 5-fold, 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 200-fold, at least about 500-fold or at least about 1000-fold. Selectivity can be measured by methods routine in the art. In some embodiments, selectivity can be tested at the  $K_m$  ATP concentration of each enzyme. In some embodiments, the selectivity of compounds of the invention can be determined by cellular assays associated with particular PI3K kinase activity.

Another aspect of the present invention pertains to methods of treating a kinase (such as PI3K)-associated disease or disorder in an individual (*e.g.*, patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of one or more compounds of the present invention or a pharmaceutical composition thereof. A PI3K-associated disease can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the PI3K, including overexpression and/or abnormal activity levels. In some embodiments, the disease can be linked to Akt (protein kinase B), mammalian target of rapamycin (mTOR), or phosphoinositide-dependent kinase 1 (PDK1). In some embodiments, the mTOR-related disease can be inflammation, atherosclerosis, psoriasis, restenosis, benign prostatic hypertrophy, bone disorders, pancreatitis, angiogenesis, diabetic retinopathy, arthritis, immunological disorders, kidney disease, or cancer. A PI3K-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating PI3K activity. In some embodiments, the disease is characterized by the abnormal activity of PI3K. In some embodiments, the disease is characterized by mutant PI3K. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

Examples of PI3K-associated diseases include immune-based diseases involving the system including, for example, rheumatoid arthritis, allergy, asthma, glomerulonephritis, lupus, or inflammation related to any of the above.

Further examples of PI3K-associated diseases include cancers such as breast, prostate, colon, endometrial, brain, bladder, skin, uterus, ovary, lung, pancreatic, renal, gastric, or hematological cancer.

In some embodiments, the hematological cancer is acute myeloblastic leukemia (AML) or chronic myeloid leukemia (CML), or B cell lymphoma.

Further examples of PI3K-associated diseases include lung diseases such as acute lung injury (ALI) and adult respiratory distress syndrome (ARDS).

Further examples of PI3K-associated diseases include osteoarthritis, restenosis, atherosclerosis, bone disorders, arthritis, diabetic retinopathy, psoriasis, benign prostatic hypertrophy, inflammation, angiogenesis, pancreatitis, kidney disease, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or Sjögren's syndrome, and the like.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a PI3K with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a PI3K, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the PI3K.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. In some embodiments, the dosage of the compound, or a pharmaceutically acceptable salt thereof, administered to a patient or individual is about 1 mg to about 2 g, or about 50 mg to about 500 mg.

As used herein, the term "treating" or "treatment" refers to one or more of (1) preventing the disease; for example, preventing 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; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the

disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating  
5 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.

#### *Combination Therapies*

10 One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, EGFR, HER2, JAK, c-MET, VEGFR, PDGFR, cKit, IGF-1R, RAF and FAK kinase inhibitors such as, for example, those described in WO 2006/056399, or other agents such as, therapeutic antibodies can be used in combination with the  
15 compounds of the present invention for treatment of PI3K-associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

Example antibodies for use in combination therapy include but are not limited to Trastuzumab (e.g. anti-HER2), Ranibizumab (e.g. anti-VEGF-A), Bevacizumab  
20 (trade name Avastin, e.g. anti-VEGF), Panitumumab (e.g. anti-EGFR), Cetuximab (e.g. anti-EGFR), Rituxan (anti-CD20) and antibodies directed to c-MET.

One or more of the following agents may be used in combination with the compounds of the present invention and are presented as a non limiting list: a  
cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan,  
25 camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoptrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec™, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine,  
30 Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-  
35 Asparaginase, Teniposide 17.alpha.-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone,

Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, 5 Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrozole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, 10 Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant, Ifosfomide, Rituximab, C225, Campath, Clofarabine, cladribine, aphidicolon, rituxan, sunitinib, dasatinib, tezacitabine, Sml1, fludarabine, pentostatin, triapine, didox, trimidox, amidox, 3-AP, and MDL-101,731.

Example chemotherapeutics include proteasome inhibitors (*e.g.*, bortezomib), 15 thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include corticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include the compounds, and pharmaceutically 20 acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and U.S. Ser. No. 60/578,491.

Example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120.

25 Example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

Example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

30 In some embodiments, the compounds of the invention can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, the compounds of the invention can be used in combination with a chemotherapeutic in the treatment of cancer, such as multiple 35 myeloma, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. Examples of

additional pharmaceutical agents used in the treatment of multiple myeloma, for example, can include, without limitation, melphalan, melphalan plus prednisone  
5 [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. Additive or synergistic effects are desirable outcomes of combining a PI3K inhibitor of the present invention with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone  
10 may be reversible upon treatment with the PI3K inhibitor of the present invention. The agents can be combined with the present compound in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, a corticosteroid such as dexamethasone is administered  
15 to a patient in combination with the compounds of the invention where the dexamethasone is administered intermittently as opposed to continuously.

In some embodiments, the compound is administered in combination with a kinase inhibitor that inhibits a kinase other than a PI3K kinase.

In some further embodiments, combinations of the compounds of the  
20 invention with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

#### *Pharmaceutical Formulations and Dosage Forms*

In some embodiments, the present invention provides a composition  
25 comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier. When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes,  
30 depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration  
35 includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular,

administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

The compounds of the 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, *e.g.*, see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth,

gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include:

5 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  
10 known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each  
15 unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compositions of the invention contain from about 5 to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 5 to about 10, about 10  
20 to about 15, about 15 to about 20, about 20 to about 25, about 25 to about 30, about 30 to about 35, about 35 to about 40, about 40 to about 45, or about 45 to about 50 mg of the active ingredient.

In some embodiments, the compositions of the invention contain from about 50 to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 50 to about 100, about  
25 100 to about 150, about 150 to about 200, about 200 to about 250, about 250 to about 300, about 350 to about 400, or about 450 to about 500 mg of the active ingredient.

In some embodiments, the compositions of the invention contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 500 to about 550,  
30 about 550 to about 600, about 600 to about 650, about 650 to about 700, about 700 to about 750, about 750 to about 800, about 800 to about 850, about 850 to about 900, about 900 to about 950, or about 950 to about 1000 mg of the active ingredient.

Similar dosages may be used of the compounds described herein in the  
35 methods and uses of the invention.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present 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, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are



administered by the oral or nasal respiratory route for local or systemic effect.

Compositions in can be nebulized by use of inert gases. Nebulized solutions may be  
5 breathed directly from the nebulizing device or the nebulizing device can be attached  
to a face mask, tent, or intermittent positive pressure breathing machine. Solution,  
suspension, or powder compositions can be administered orally or nasally from  
devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some  
10 embodiments, ointments can contain water and one or more hydrophobic carriers  
selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene  
glycol, white Vaseline, and the like. Carrier compositions of creams can be based on  
water in combination with glycerol and one or more other components, e.g.  
glycerinmonostearate, PEG-glycerinmonostearate and cetylstearyl alcohol. Gels can  
15 be formulated using isopropyl alcohol and water, suitably in combination with other  
components such as, for example, glycerol, hydroxyethyl cellulose, and the like. In  
some embodiments, topical formulations contain at least about 0.1, at least about 0.25,  
at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the  
compound of the invention. The topical formulations can be suitably packaged in  
20 tubes of, for example, 100 g which are optionally associated with instructions for the  
treatment of the select indication, e.g., psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary  
depending upon what is being administered, the purpose of the administration, such as  
prophylaxis or therapy, the state of the patient, the manner of administration, and the  
25 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  
30 condition of the patient, and the like.

The compositions administered to a patient can be in the form of  
pharmaceutical compositions described above. These compositions can be sterilized  
by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions  
can be packaged for use as is, or lyophilized, the lyophilized preparation being  
35 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

5 pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a  
10 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  
15 from about 1  $\mu\text{g}/\text{kg}$  to about 1  $\text{g}/\text{kg}$  of body weight per day. In some embodiments, the dose range is from about 0.01  $\text{mg}/\text{kg}$  to about 100  $\text{mg}/\text{kg}$  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  
20 route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compositions of the invention can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed hereinabove.

25

#### *Labeled Compounds and Assay Methods*

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  
30 quantitating PI3K in tissue samples, including human, and for identifying PI3K ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes PI3K assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An “isotopically” or “radio-labeled” compound is a compound of the  
35 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). Suitable radionuclides that may be  
5 incorporated in compounds of the present invention include but are not limited to  $^2\text{H}$  (also written as D for deuterium),  $^3\text{H}$  (also written as T for tritium),  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{13}\text{N}$ ,  $^{15}\text{N}$ ,  $^{15}\text{O}$ ,  $^{17}\text{O}$ ,  $^{18}\text{O}$ ,  $^{18}\text{F}$ ,  $^{35}\text{S}$ ,  $^{36}\text{Cl}$ ,  $^{82}\text{Br}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$ ,  $^{77}\text{Br}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$  and  $^{131}\text{I}$ . 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*  
10 PI3K labeling and competition assays, compounds that incorporate  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{82}\text{Br}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or will generally be most useful. For radio-imaging applications  $^{11}\text{C}$ ,  $^{18}\text{F}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{131}\text{I}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$  or  $^{77}\text{Br}$  will generally be most useful.

It is understood that a “radio-labeled ” or “labeled compound” is a compound that has incorporated at least one radionuclide. In some embodiments the  
15 radionuclide is selected from the group consisting of  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{125}\text{I}$ ,  $^{35}\text{S}$  and  $^{82}\text{Br}$ .

The present invention can further include synthetic methods for incorporating radio-isotopes into compounds of the invention. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of  
20 invention.

A labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a PI3K by monitoring its concentration variation when contacting with the PI3K,  
25 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 PI3K (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the PI3K directly correlates to its binding affinity. Conversely, in some other screening assays, the standard  
30 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.

35 *Kits*

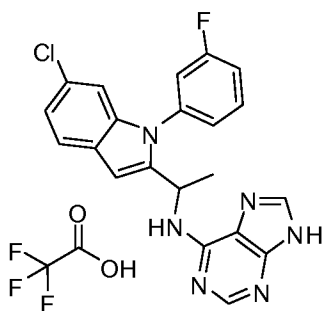
The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of PI3K-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to be PI3K inhibitors according to at least one assay described herein.

### EXAMPLES

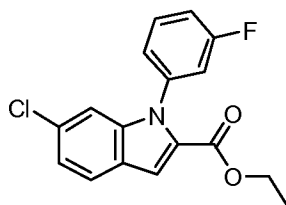
The example compounds below containing one or more chiral centers were obtained in racemate form or as isomeric mixtures, unless otherwise specified.

**Example 1. *N*-{1-[6-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate**



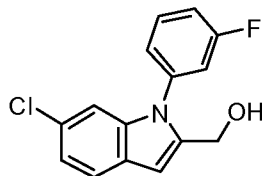
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*Step 1. Ethyl 6-chloro-1-(3-fluorophenyl)-1H-indole-2-carboxylate*



Activated molecular sieves (8.9 g) 4Å were placed in an oven dried round  
 10 bottom flask and cooled to room temperature under nitrogen. Ethyl 6-chloro-1H-indole-2-carboxylate (from AsymChem, 0.500 g, 2.24 mmol), (3-fluorophenyl)boronic acid (0.938 g, 6.71 mmol), copper acetate (0.40 g, 3.3 mmol), methylene chloride (80 mL) was added to the flask, followed by pyridine (0.723 mL, 8.94 mmol). The reaction mixture was stirred at room temperature for 2 days, and  
 15 then filtered through Celite. The filtrate was concentrated under reduced pressure. The resultant residue was purified by chromatography on silica gel (eluting with 0 to 50% EtOAc in hexane) to give the desired product (0.60 g). LCMS calculated for  $C_{17}H_{14}ClFNO_2(M+H)^+$ :  $m/z = 318.1$ ; Found: 318.1.

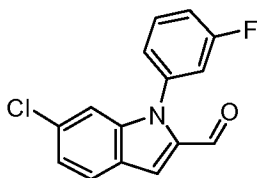
20 *Step 2. [6-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]methanol*



A solution of ethyl 6-chloro-1-(3-fluorophenyl)-1H-indole-2-carboxylate (0.60 g, 1.9 mmol) in tetrahydrofuran (10 mL) was cooled at -78 °C. Lithium

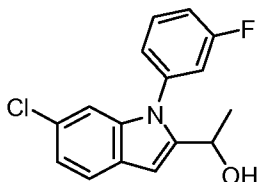
tetrahydroaluminate (1 M) in tetrahydrofuran (6.0 mL, 6.0 mmol) was added dropwise and the resulting mixture was stirred at this temperature for 1 hour. The reaction was  
5 quenched by the addition of water (0.12 mL) and stirred for 10 minutes, warmed up to room temperature, followed by the addition of 5% aqueous NaOH solution (0.12 mL) with stirring for 10 minutes. Then additional water (0.36 mL) was added and stirring was continued for 10 minutes. The mixture was filtered, dried over MgSO<sub>4</sub> and concentrated to give the crude product (0.53 g). The residue was used in the next step  
10 directly. LCMS calculated for C<sub>15</sub>H<sub>12</sub>ClFNO(M+H)<sup>+</sup>: m/z = 276.1; Found: 276.0.

*Step 3. 6-Chloro-1-(3-fluorophenyl)-1H-indole-2-carbaldehyde*



Dess-Martin periodinane (1.3 g, 2.9 mmol) was added to a solution of [6-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]methanol (0.53 g, 1.9 mmol) in methylene  
15 chloride (10 mL). The solution was stirred at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane, washed with 1:1 aqueous saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and NaHCO<sub>3</sub>. The organic layers were dried over MgSO<sub>4</sub>, concentrated and purified on silica gel (eluting with 0-20% EtOAc in hexane) to give  
20 the desired product (50 mg). LCMS calculated for C<sub>15</sub>H<sub>10</sub>ClFNO(M+H)<sup>+</sup>: m/z = 274.0; Found: 274.0.

*Step 4. 1-[6-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanol*

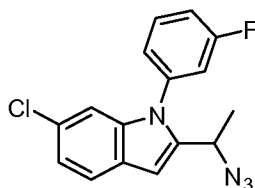


To a mixture of 6-chloro-1-(3-fluorophenyl)-1H-indole-2-carbaldehyde (50  
25 mg, 0.18 mmol) in tetrahydrofuran (5 mL) was added 3.0 M methylmagnesium bromide in ether (0.091 mL, 0.27 mmol). The reaction was stirred at room temperature for 1 hour, quenched with water, and then extracted with ethyl acetate (EtOAc). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>  
30 and concentrated to give the desired product (51 mg). The crude product was used

directly in next step. LCMS calculated for  $C_{16}H_{14}ClFNO(M+H)^+$ :  $m/z = 290.1$ ;  
Found: 289.7.

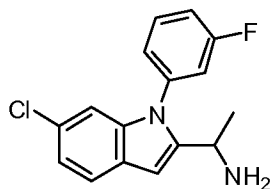
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*Step 5. 2-(1-azidoethyl)-6-chloro-1-(3-fluorophenyl)-1H-indole*



To a mixture of 1-[6-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanol (51 mg, 0.18 mmol) and *N,N*-diisopropylethylamine (0.046 mL, 0.26 mmol) in  
10 dichloromethane (3 mL) was added methanesulfonyl chloride (0.018 mL, 0.23 mmol).  
The reaction was stirred at room temperature for 1 hour, quenched with water, and  
then extracted with dichloromethane. The organic layers were combined, washed with  
brine, dried over  $MgSO_4$  and concentrated to give corresponding mesylate. LCMS  
[M- $MsO$ ] $^+$   $m/z = 272.0$ . To the crude 1-[6-chloro-1-(3-fluorophenyl)-1H-indol-  
15 2-yl]ethyl methanesulfonate in *N,N*-dimethylformamide (1 mL) was added sodium  
azide (57 mg, 0.88 mmol). The reaction was stirred at room temperature for 2 hours,  
quenched with water, and then extracted with EtOAc. The extracts were combined,  
washed with brine, dried over  $MgSO_4$  and concentrated to give the desired azide (55  
mg), which was used directly in the next step. LCMS calculated for  $C_{16}H_{12}ClFN(M-$   
20  $N_3)^+$ :  $m/z = 272.1$ ; Found: 271.9.

*Step 6. 1-[6-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine*



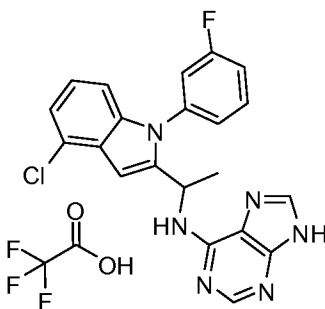
To a solution of 2-(1-azidoethyl)-6-chloro-1-(3-fluorophenyl)-1H-indole (55  
25 mg, 0.17 mmol) in tetrahydrofuran (2 mL) was added 1.00 M of trimethylphosphine  
in tetrahydrofuran (0.26 mL, 0.26 mmol) and the resultant mixture was stirred at room  
temperature for 1 hour. The mixture was concentrated to give the desired amine (50  
mg). The crude product was used directly in the next step. LCMS calculated for  
 $C_{16}H_{12}ClFN(M-NH_2)^+$ :  $m/z = 272.1$ ; Found: 272.0.

30

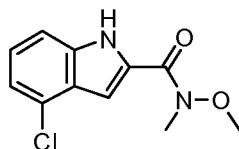
*Step 7. N-{1-[6-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine*

5 A mixture of 1-[6-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine (50 mg, 0.17 mmol), 6-bromo-9H-purine (52 mg, 0.26 mmol) and *N,N*-diisopropylethylamine (0.060 mL, 0.35 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was cooled and then filtered. The filtrate was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5 μM; eluting with a gradient  
10 of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a TFA salt. LCMS calculated for  $C_{21}H_{17}ClFN_6(M+H)^+$ :  $m/z = 407.1$ ; Found: 407.0.

**Example 2. *N*-{1-[4-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate**



*Step 1. 4-Chloro-N-methoxy-N-methyl-1H-indole-2-carboxamide*

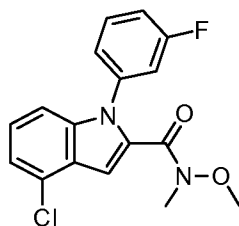


20 A mixture of 4-chloro-1H-indole-2-carboxylic acid (from Ryan Scientific, 1.0 g, 5.1 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (2.9 g, 7.7 mmol) and triethylamine (3.6 mL, 26 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at room temperature for 10 minutes. *N,O*-Dimethylhydroxylamine hydrochloride (0.75 g, 7.7 mmol) was added and the  
25 resulting suspension was stirred at room temperature overnight. The mixture was quenched with water and then extracted with EtOAc. The combined organic layers were dried over  $MgSO_4$ , concentrated and purified on silica gel (eluting with 0-35% EtOAc in hexane) to give the desired product (0.35 g, 29%). LCMS calculated for



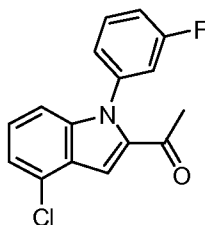
$C_{11}H_{12}ClN_2O_2(M+H)^+$ :  $m/z = 239.1$ ; Found: 239.1.

5            *Step 2. 4-Chloro-1-(3-fluorophenyl)-N-methoxy-N-methyl-1H-indole-2-carboxamide*



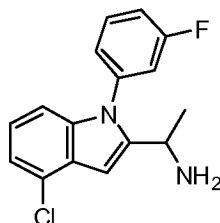
Activated molecular sieves (4.9 g) 4Å were placed in an oven dried flask and cooled to room temperature under nitrogen. To the flask was charged with 4-chloro-  
10 *N*-methoxy-*N*-methyl-1H-indole-2-carboxamide (0.35 g, 1.5 mmol), (3-fluorophenyl)boronic acid (0.62 g, 4.4 mmol) and cupric acetate (0.40 g, 2.2 mmol), methylene chloride (65 mL) and then pyridine (0.47 mL, 5.9 mmol). The reaction mixture was stirred at room temperature overnight, then filtered through a pad of Celite. The filtrate was concentrated and purified on silica gel (eluting with 0-20%  
15 EtOAc in hexane) to give the desired product (0.44 g, 90%). LCMS calculated for  $C_{17}H_{15}ClFN_2O_2(M+H)^+$ :  $m/z = 333.1$ ; Found: 333.0.

*Step 3. 1-[4-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanone*



20            To a mixture of 4-chloro-1-(3-fluorophenyl)-*N*-methoxy-*N*-methyl-1H-indole-2-carboxamide (0.44 g, 1.3 mmol) in tetrahydrofuran (10 mL) was added 1.4 M methylmagnesium bromide in tetrahydrofuran (4.7 mL, 6.6 mmol) dropwise. The reaction was stirred at room temperature overnight, then quenched with aqueous saturated  $NH_4Cl$  solution and extracted with EtOAc. The extracts were dried over  
25  $MgSO_4$ , concentrated and purified on silica gel (eluting with 0-10% EtOAc in hexane) to give the desired product (0.26 g, 68%). LCMS calculated for  $C_{16}H_{12}ClFNO(M+H)^+$ :  $m/z = 288.1$ ; Found: 288.0.

Step 4. 1-[4-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine



5 A mixture of 1-[4-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanone (0.13 g, 0.45 mmol) and ammonium acetate (0.348 g, 4.52 mmol) in methanol (2.0 mL) and acetonitrile (2.0 mL) was heated at 65 °C in a sealed tube for 30 minutes. After cooling to room temperature, to the resultant mixture was added sodium cyanoborohydride (57 mg, 0.91 mmol). The reaction was heated at 65 °C for another  
 10 4 hours. After cooling to room temperature, the reaction was quenched with aqueous saturated NaHCO<sub>3</sub> solution and then extracted with dichloromethane. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated to give the desired product (0.11 g), which was used directly in the next step. LCMS calculated for C<sub>16</sub>H<sub>12</sub>ClFN(M-NH<sub>2</sub>)<sup>+</sup>: m/z = 272.1; Found: 272.0.

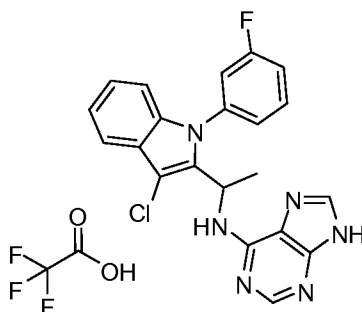
15

Step 5. N-{1-[4-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine

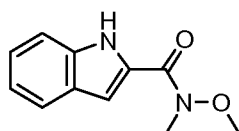
A mixture of 1-[4-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine (0.11 g, 0.38 mmol), 6-bromo-9H-purine (0.11 g, 0.57 mmol) and *N,N*-diisopropylethylamine (0.20 mL, 1.1 mmol) in ethanol (1.5 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5 μM; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a TFA salt. LCMS calculated for  
 25 C<sub>21</sub>H<sub>17</sub>ClFN<sub>6</sub>(M+H)<sup>+</sup>: m/z = 407.2; Found: 407.0. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.81 (1H, br s), 8.36 (1H, s), 8.31 (1H, m), 7.51 (1H, m), 7.35 (1H, m), 7.20 (1H, m), 7.16 (1H, d, *J* = 7.6 Hz), 7.09 (1H, dd, *J* = 8.0 and 7.6 Hz), 6.96 (1H, d, *J* = 8.0 Hz), 6.78 (1H, s), 5.58 (1H, m), 1.60 (3H, d, *J* = 6.4 Hz) ppm. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 376.3 MHz) for the TFA salt: δ -74.7, -111.4 (0.5 F) and -112.0 (0.5 F) ppm.

30

**Example 3. N-{1-[3-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate**

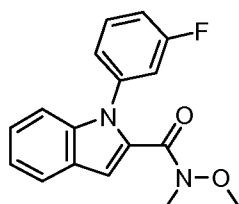


5 *Step 1. N-Methoxy-N-methyl-1H-indole-2-carboxamide*



A mixture of 1H-indole-2-carboxylic acid (from Aldrich, 2.5 g, 16 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (7.6 g, 20 mmol) and triethylamine (11 mL, 78 mmol) in *N,N*-dimethylformamide (20 mL) was stirred at room temperature for 10 minutes. *N,O*-Dimethylhydroxylamine hydrochloride (2.0 g, 20 mmol) was added and the resulting suspension was stirred at room temperature for 2 hours. The mixture was quenched with water, extracted with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified on silica gel (eluting with 0-50% EtOAc in hexane) to give the desired product (2.7 g, 85%). LCMS calculated for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 205.1: Found: 205.1.

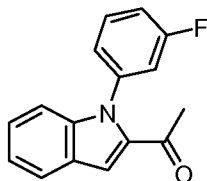
*Step 2. 1-(3-Fluorophenyl)-N-methoxy-N-methyl-1H-indole-2-carboxamide*



20 Activated molecular sieves (6.0 g) 4Å were placed in an oven dried flask and cooled to room temperature under nitrogen. To the flask was charged with *N*-methoxy-*N*-methyl-1H-indole-2-carboxamide (0.45 g, 2.2 mmol), (3-fluorophenyl)boronic acid (0.94 g, 6.7 mmol), cupric acetate (0.60 g, 3.3 mmol), and methylene chloride (80 mL) and then pyridine (0.72 mL, 8.9 mmol). The reaction mixture was stirred at room temperature over weekend, then filtered through a pad of

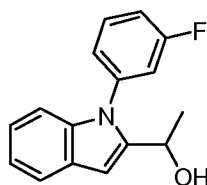
Celite. The filtrate was concentrated and purified on silica gel (eluting with 0-25% EtOAc in hexane) to give the title compound (0.30 g, 46%). LCMS calculated for  $C_{17}H_{16}FN_2O_2(M+H)^+$ :  $m/z = 299.1$ ; Found: 299.0.

*Step 3. 1-[1-(3-Fluorophenyl)-1H-indol-2-yl]ethanone*



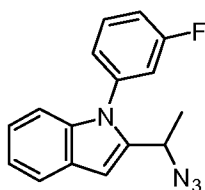
To a mixture of 1-(3-fluorophenyl)-*N*-methoxy-*N*-methyl-1H-indole-2-carboxamide (0.30 g, 1.0 mmol) in tetrahydrofuran (6 mL) was added 1.4 M methylmagnesium bromide in tetrahydrofuran (1.1 mL, 1.5 mmol). The reaction was stirred at room temperature for 2 hours, then quenched with saturated  $NH_4Cl$  solution, extracted with EtOAc. The combined organic layers were washed with brine, dried over  $MgSO_4$  and concentrated to give the desired product (0.27 g). The crude product was used directly in next step. LCMS calculated for  $C_{16}H_{13}FNO(M+H)^+$ :  $m/z = 254.1$ ; Found: 254.1.

*Step 4. 1-[1-(3-Fluorophenyl)-1H-indol-2-yl]ethanol*



To a mixture of 1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethanone (0.27 g, 1.1 mmol) in methanol (6 mL) was added sodium tetrahydroborate (41 mg, 1.1 mmol). The reaction was stirred at room temperature for 1 hour, quenched with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over  $MgSO_4$  and concentrated to give title compound (0.26 g). The crude product was used directly in the next step. LCMS calculated for  $C_{16}H_{13}FN(M-OH)^+$ :  $m/z = 238.1$ ; Found: 238.1.

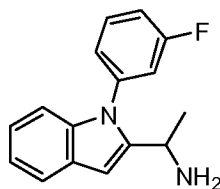
*Step 5. 2-(1-Azidoethyl)-1-(3-fluorophenyl)-1H-indole*



To a mixture of 1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethanol (0.26 g, 1.0 mmol) and *N,N*-diisopropylethylamine (0.27 mL, 1.5 mmol) in dichloromethane (6 mL) was added methanesulfonyl chloride (0.10 mL, 1.3 mmol). The reaction was stirred at room temperature for 1 hour, quenched with water, and extracted with dichloromethane. The combined extracts were washed with brine, dried over  $\text{MgSO}_4$  and concentrated to give corresponding mesylate which was used directly in the next step. LCMS  $[\text{M}-\text{MsO}]^+$   $m/z = 238.1$ .

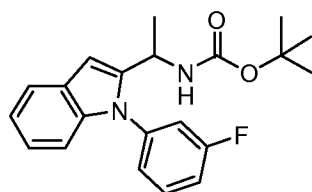
To the crude 1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethyl methanesulfonate in *N,N*-dimethylformamide (5 mL) was added sodium azide (0.20 g, 3.0 mmol). The reaction was stirred at room temperature for 2 hr, quenched with water, and extracted with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$ , concentrated and purified on silica gel (eluting with 0-30% EtOAc in hexane) to give the desired product (0.14 g, 49%). LCMS calculated for  $\text{C}_{16}\text{H}_{13}\text{FN}(\text{M}-\text{N}_3)^+$ :  $m/z = 238.1$ ; Found: 238.1.

*Step 6. 1-[1-(3-Fluorophenyl)-1H-indol-2-yl]ethanamine*



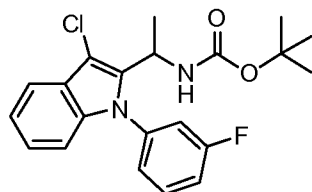
To a solution of 2-(1-azidoethyl)-1-(3-fluorophenyl)-1H-indole (0.14 g, 0.50 mmol) in tetrahydrofuran (3 mL) was added 1.00 M trimethylphosphine in tetrahydrofuran (0.75 mL, 0.75 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give crude product (0.17 g), which was used directly in the next step. LCMS calculated for  $\text{C}_{16}\text{H}_{13}\text{FN}(\text{M}-\text{NH}_2)^+$ :  $m/z = 238.1$ ; Found: 238.1.

*Step 7. tert-Butyl {1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}carbamate*



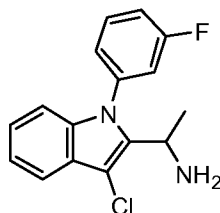
Di-*tert*-butyldicarbonate (0.23 mL, 1.0 mmol) was added to a mixture of 1-[1-  
 5 (3-fluorophenyl)-1H-indol-2-yl]ethanamine (0.17 g, 0.67 mmol) and triethylamine  
 (0.46 mL, 3.3 mmol) in tetrahydrofuran (3 mL). After 30 minutes, the mixture was  
 quenched with saturated NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic  
 layers were dried over MgSO<sub>4</sub>, concentrated, and purified on silica gel (eluting with  
 0-20% EtOAc in hexane) to give the desired product (35 mg). LCMS calculated for  
 10 C<sub>21</sub>H<sub>24</sub>FN<sub>2</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 355.2; Found: 355.1.

*Step 8. tert-Butyl {1-[3-chloro-1-(3-fluorophenyl)-1H-indol-2-  
 yl]ethyl}carbamate*



15 A solution of *N*-chlorosuccinimide (0.015 g, 0.11 mmol) in DMF (0.1 mL)  
 was added dropwise to an ice-cooled solution of *tert*-butyl {1-[1-(3-fluorophenyl)-1H-  
 indol-2-yl]ethyl}carbamate (35 mg, 0.099 mmol) in *N,N*-dimethylformamide (0.5 mL,  
 6 mmol). The resulting mixture was allowed to warm to room temperature and stirred  
 for an additional 4 hours. The mixture was then diluted with water and then extracted  
 20 with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, concentrated, and  
 purified on silica gel (eluting with 0-10% EtOAc in hexane) to give the desired  
 product (36 mg, 94%).

*Step 9. 1-[3-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine*



25

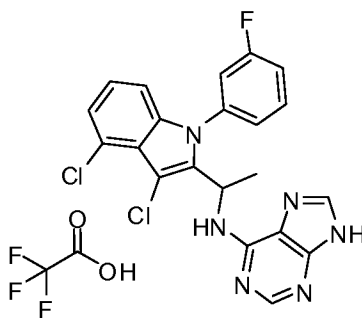
Hydrogen chloride (4.0 M) in 1,4-dioxane (0.5 mL, 20 mmol) was added to a

solution of *tert*-butyl {1-[3-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl} carbamate (36 mg, 0.092 mmol) in 1,4-dioxane (1.0 mL) and the reaction was stirred at room temperature for 1 hour. The mixture was diluted with EtOAc, washed with saturated NaHCO<sub>3</sub> solution and water. The combined extracts were dried over MgSO<sub>4</sub> and concentrated to give the desired product (31.5 mg). LCMS calculated for C<sub>16</sub>H<sub>12</sub>ClFN(M-NH<sub>2</sub>)<sup>+</sup>: m/z = 272.1; Found: 272.0.

10 *Step 10. N-{1-[3-Chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine*

A mixture of 1-[3-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine (31 mg, 0.11 mmol), 6-bromo-9H-purine (32 mg, 0.16 mmol) and *N,N*-diisopropylethylamine (0.056 mL, 0.32 mmol) in ethanol (1.0 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5 μM; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a TFA salt. LCMS calculated for C<sub>21</sub>H<sub>17</sub>ClFN<sub>6</sub>(M+H)<sup>+</sup>: m/z = 407.1; Found: 407.0. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.69 (1H, br s), 8.36 (1H, s), 8.33 (1H, m), 7.68 (1H, m), 7.60 (1H, m), 7.47 (1H, m), 7.41 (1H, m), 7.29 (1H, d, *J* = 7.6 Hz), 7.16 (2H, m), 6.98 (1H, m), 5.25 (1H, m), 1.70 (3H, m) ppm. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 376.3 MHz) for the TFA salt: δ -74.6, -111.6 ppm.

25 **Example 4. *N*-{1-[3,4-Dichloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate**

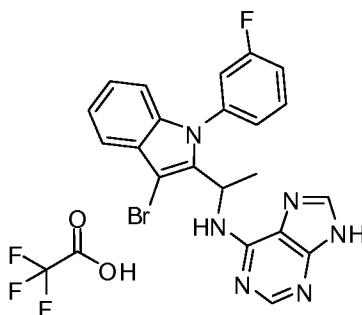


A mixture of *N*-{1-[4-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine (40 mg, 0.099 mmol) and *N*-chlorosuccinimide (15 mg, 0.11 mmol) in *N,N*-dimethylformamide (0.5 mL) was stirred at room temperature overnight. The

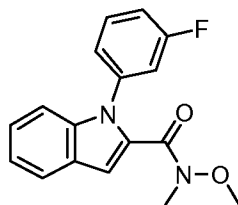
mixture was purified with preparative-LCMS (XBridge C18 column, 19x100 mm, 5  
 μM; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate  
 5 30 mL/min; with injection volume of 2 mL) to give the desired product as a TFA salt.  
 LCMS calculated for C<sub>21</sub>H<sub>16</sub>Cl<sub>2</sub>FN<sub>6</sub>(M+H)<sup>+</sup>: m/z = 441.1; Found: 441.0. <sup>1</sup>H NMR  
 (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.76 (1H, br s), 8.38 (2H, m), 7.71 (1H, m), 7.57 (1H, m),  
 7.43 (2H, m), 7.12 (2H, m), 6.89 (1H, m), 5.18 (1H, m), 1.71 (3H, m) ppm. <sup>19</sup>F NMR  
 (DMSO-*d*<sub>6</sub>, 376.3 MHz) for the TFA salt: δ -74.7, -111.5 (0.5 F), -111.6 (0.5 F) ppm.

10

**Example 5. *N*-{1-[3-Bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate**



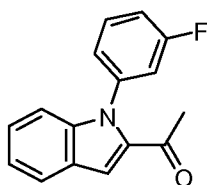
15 *Step 1. 1-(3-Fluorophenyl)-N-methoxy-N-methyl-1H-indole-2-carboxamide*



Activated molecular sieves (13 g) 4Å were placed in an oven dried round  
 bottom flask and cooled to room temperature under nitrogen. To the flask was  
 charged with *N*-methoxy-*N*-methyl-1H-indole-2-carboxamide (0.97 g, 4.7 mmol), (3-  
 20 fluorophenyl)- boronic acid (1.5 g, 11 mmol), cupric acetate (1.3 g, 7.3 mmol),  
 methylene chloride (130 mL) and then pyridine (1.5 mL, 19 mmol). The reaction  
 mixture was stirred at room temperature over the weekend. The mixture was filtered  
 through a pad of Celite. The filtrate was concentrated and purified on silica gel  
 (eluting with 0-30% EtOAc/hexane) to give the title compound (0.52 g, 37%). LCMS  
 25 calculated for C<sub>17</sub>H<sub>16</sub>FN<sub>2</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 299.1; Found: 299.1.

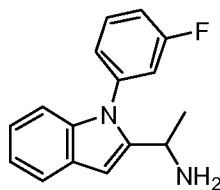
*Step 2. 1-[1-(3-Fluorophenyl)-1H-indol-2-yl]ethanone*





To a mixture of 1-(3-fluorophenyl)-*N*-methoxy-*N*-methyl-1H-indole-2-  
5 carboxamide (0.52 g, 1.7 mmol) in tetrahydrofuran (10 mL) was added 3.0 M  
methylmagnesium bromide in ether (4.6 mL, 0.014 mol). The reaction was stirred at  
room temperature overnight. The reaction was quenched with saturated NH<sub>4</sub>Cl  
solution and extracted with EtOAc. The combined organic layers were washed with  
water and brine, dried over MgSO<sub>4</sub>, and concentrated to give crude product (0.4 g,  
10 91%). The crude product was used directly in next step. LCMS calculated for  
C<sub>16</sub>H<sub>13</sub>FNO(M+H)<sup>+</sup>: m/z = 254.1; Found: 254.1.

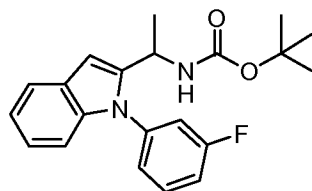
*Step 3. 1-[1-(3-Fluorophenyl)-1H-indol-2-yl]ethanamine*



A mixture of 1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethanone (0.40 g, 1.6  
15 mmol) and ammonium acetate (1.22 g, 15.8 mmol) in methanol (5.0 mL) and  
acetonitrile (5.0 mL) was heated at 65 °C in a sealed tube for 30 minutes. After  
cooling to room temperature, sodium cyanoborohydride (0.20 g, 3.2 mmol) was added  
to the resultant mixture. The reaction was heated at 65 °C overnight. The reaction was  
20 cooled to room temperature and quenched with saturated NaHCO<sub>3</sub> solution and  
extracted with dichloromethane. The combined organic layers were dried over  
MgSO<sub>4</sub> and concentrated to give crude product (0.39 g, 97%), which was used  
directly in the next step. LCMS calculated for C<sub>16</sub>H<sub>13</sub>FN (M-NH<sub>2</sub>)<sup>+</sup>: m/z = 238.1;  
Found: 238.1.

25

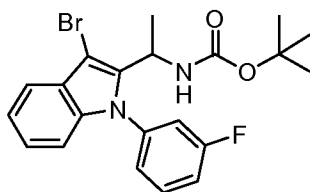
*Step 4. tert-Butyl {1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}carbamate*



Di-*tert*-butyldicarbonate (1.4 g, 6.4 mmol) was added to a mixture of 1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine (0.39 g, 1.5 mmol) and triethylamine (1.8 mL, 13 mmol) in tetrahydrofuran (8 mL). After 30 min, the mixture was quenched with saturated NaHCO<sub>3</sub> solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, concentrated, and purified on silica gel (eluting with 0-20% EtOAc/hexane) to give the desired product (0.41 g, 75%). LCMS calculated for C<sub>21</sub>H<sub>24</sub>FN<sub>2</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 355.2; Found: 355.1.

10

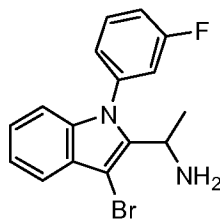
*Step 5. tert-Butyl {1-[3-bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}carbamate*



A solution of *N*-bromosuccinimide (0.24 g, 1.3 mmol) in DMF (1 mL) was added dropwise to an ice-cooled solution of *tert*-butyl {1-[1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}carbamate (0.41 g, 1.2 mmol) in *N,N*-dimethylformamide (5 mL). The resulting mixture was allowed to warm to room temperature and stirred for an additional 4 hours. The mixture was diluted with water and extracted with EtOAc. The extracts were combined, dried over MgSO<sub>4</sub>, concentrated, and purified on silica gel (eluting with 0-10% EtOAc/hexane) to give the desired product (0.34g, 68%). LCMS calculated for C<sub>21</sub>H<sub>22</sub>BrFN<sub>2</sub>O<sub>2</sub>Na(M+Na)<sup>+</sup>: m/z = 455.1; Found: 455.0.

20

*Step 6. 1-[3-Bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine*



Hydrogen chloride (4.0 M) in 1,4-dioxane (1.2 mL, 4.8 mmol) was added to a solution of *tert*-butyl {1-[3-bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}carbamate (0.15 g, 0.35 mmol) in 1,4-dioxane (2.0 mL). The reaction was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc, washed with saturated NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub> and concentrated to give the crude product (0.12

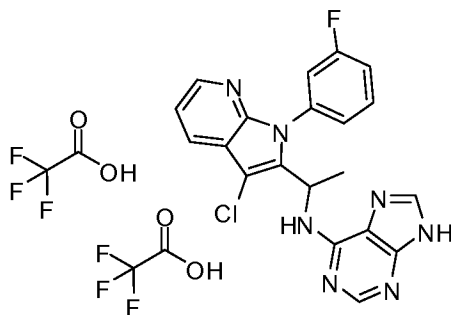
25

g). LCMS calculated for  $C_{16}H_{12}BrFN$  ( $M-NH_2$ )<sup>+</sup>:  $m/z = 316.0$ ; Found: 316.0.

5 *Step 7. N-{1-[3-Bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate*

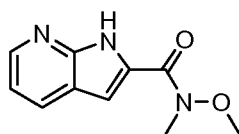
A mixture of 1-[3-bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethanamine (0.12 g, 0.36 mmol), 6-bromo-9H-purine (0.11 g, 0.54 mmol) and *N,N*-diisopropylethylamine (0.19 mL, 1.1 mmol) in ethanol (2.0 mL) was heated at 110 °C  
 10 overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5 μM; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired compound as a TFA salt. LCMS calculated for  $C_{21}H_{17}BrFN_6$  ( $M+H$ )<sup>+</sup>:  $m/z = 451.1$ ; Found: 451.0. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ  
 15 7.84 (1H, s), 7.70 (1H, m), 7.62 (1H, m), 7.45 (2H, m), 7.39 (2H, m), 7.15 (2H, m), 6.97 (1H, m), 5.34 (1H, m), 1.59 (3H, m) ppm.

**Example 6. N-{1-[3-Chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}-9H-purin-6-amine bis(trifluoroacetate)**



20

*Step 1. N-Methoxy-N-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide*

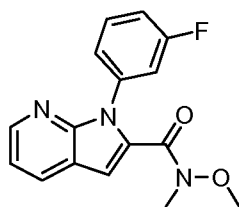


A mixture of 1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (from MolBridge, 1.0 g, 6.2 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (3.0 g, 8.0 mmol) and triethylamine (4.3 mL, 31 mmol) in *N,N*-dimethylformamide (10 mL) was stirred at room temperature for 10 minutes. *N,O*-dimethylhydroxylamine hydrochloride (0.78 g, 8.0 mmol) was added and the resulting

25

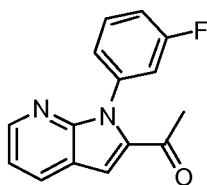
suspension was stirred at room temperature overnight. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over  
 5 MgSO<sub>4</sub>, concentrated, and purified on silica gel (eluting with 0-65% EtOAc/hexane) to give the desired product (1.0 g, 79%). LCMS calculated for C<sub>10</sub>H<sub>12</sub>N<sub>3</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 206.1; Found: 206.1.

10 *Step 2. 1-(3-Fluorophenyl)-N-methoxy-N-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide*



Activated molecular sieves (3.8 g) 4Å were placed in an oven dried flask and cooled to room temperature under nitrogen. To the flask was charged with *N*-methoxy-*N*-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (0.29 g, 1.4 mmol), (3-  
 15 fluorophenyl)boronic acid (0.59 g, 4.2 mmol), cupric acetate (0.38 g, 2.1 mmol), methylene chloride (35 mL) and then pyridine (0.46 mL, 5.6 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite. The filtrate was concentrated and purified on silica gel (eluting with 0-50% EtOAc/hexane followed by 0-5% MeOH/dichloromethane) to give the desired  
 20 product (0.35 g, 83%). LCMS calculated for C<sub>16</sub>H<sub>15</sub>FN<sub>3</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 300.1; Found: 300.0.

*Step 3. 1-[1-(3-Fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanone*

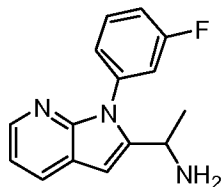


25 To a mixture of 1-(3-fluorophenyl)-*N*-methoxy-*N*-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (0.35 g, 1.2 mmol) in tetrahydrofuran (10 mL) was added 3.0 M methylmagnesium bromide in ether (3.1 mL, 9.4 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with saturated NH<sub>4</sub>Cl solution and then extracted with EtOAc. The combined organic layers were

washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated to give the desired product (0.24 g, 81%). The crude product was used directly in next step. LCMS

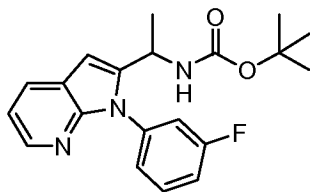
5 calculated for  $\text{C}_{15}\text{H}_{12}\text{FN}_2\text{O}(\text{M}+\text{H})^+$ :  $m/z = 255.1$ ; Found: 255.1.

*Step 4. 1-[1-(3-Fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanamine*



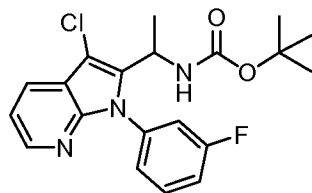
A mixture of 1-[1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanone  
 10 (0.24 g, 0.94 mmol) and ammonium acetate (0.73 g, 9.5 mmol) in methanol (3.0 mL)  
 and acetonitrile (3.0 mL) was heated at 65 °C in a sealed tube for 1 hour. After  
 cooling to room temperature, sodium cyanoborohydride (0.18 g, 2.8 mmol) was added  
 to the resultant mixture. The reaction was heated at 65 °C overnight. The reaction was  
 then cooled to room temperature and quenched with saturated  $\text{NaHCO}_3$  solution and  
 15 then extracted with dichloromethane. The combined organic layers were dried over  
 $\text{MgSO}_4$  and concentrated to give the crude amine (0.32 g), which was used directly in  
 the next step. LCMS calculated for  $\text{C}_{15}\text{H}_{15}\text{FN}_3(\text{M}+\text{H})^+$ :  $m/z = 256.1$ ; Found: 256.1.

*Step 5. tert-Butyl {1-[1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}carbamate*



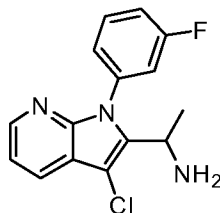
Di-*tert*-butyldicarbonate (0.82 g, 3.8 mmol) was added to a mixture of 1-[1-(3-  
 fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanamine (0.24 g, 0.94 mmol) and  
 triethylamine (1.0 mL, 7.5 mmol) in tetrahydrofuran (8 mL). After 30 minutes, the  
 25 mixture was quenched with saturated  $\text{NaHCO}_3$  solution and then extracted with  
 EtOAc. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ ,  
 concentrated and purified on silica gel (eluting with 0-5% MeOH/dichloromethane) to  
 give the desired product (0.16 g, 48%). LCMS calculated for  $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_2(\text{M}+\text{H})^+$ :  
 $m/z = 356.2$ ; Found: 356.1.

Step 6. *tert*-Butyl {1-[3-chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}carbamate



A solution of *N*-chlorosuccinimide (24 mg, 0.18 mmol) in DMF (0.1 mL) was added dropwise to an ice-cooled solution of *tert*-butyl {1-[1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}carbamate (60 mg, 0.17 mmol) (5073-171) in *N,N*-dimethylformamide (1 mL). The resulting mixture was allowed to warm to room temperature and stirred overnight. The mix was diluted with water and extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, concentrated, and purified on silica gel (eluting with 0-10% EtOAc/hexane) to give the desired product (26 mg, 40%). LCMS calculated for C<sub>20</sub>H<sub>22</sub>ClFN<sub>3</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 390.1; Found: 390.1.

Step 7. 1-[3-Chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanamine



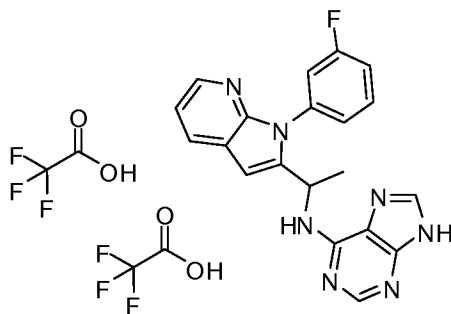
4.0 M Hydrogen chloride in 1,4-dioxane (1.0 mL, 4.0 mmol) was added to a solution of *tert*-butyl {1-[3-chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}carbamate (26 mg, 0.067 mmol) in 1,4-dioxane (1.0 mL). The reaction was stirred at room temperature overnight. The mixture was then partitioned between EtOAc and water. The aqueous layer was adjusted to pH 9 with saturated NaHCO<sub>3</sub> solution and then extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated to give the desired amine (7 mg, 40%). LCMS calculated for C<sub>15</sub>H<sub>14</sub>ClFN<sub>3</sub>(M+H)<sup>+</sup>: m/z = 290.1; Found: 290.0.

Step 8. *N*-{1-[3-Chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-

*yl]ethyl}-9H-purin-6-amine tris(trifluoroacetate)*

A mixture of 1-[3-chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanamine (7.0 mg, 0.024 mmol), 6-bromo-9H-purine (7.2 mg, 0.036 mmol) and *N,N*-diisopropylethylamine (0.013 mL, 0.072 mmol) in ethanol (0.6 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5 μM; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a bis TFA salt. LCMS calculated for C<sub>20</sub>H<sub>16</sub>ClFN<sub>7</sub>(M+H)<sup>+</sup>: m/z = 408.1; Found: 408.0. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.36 (2H, m), 8.23 (1H, m), 7.91 (1H, m), 7.59 (2H, m), 7.48 (1H, m), 7.38 (1H, m), 7.23 (1H, m), 5.27 (1H, m), 1.71 (3H, d, *J* = 6.8 Hz) ppm. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 376.3 MHz) for the TFA salt: δ -74.7, -112.5 ppm.

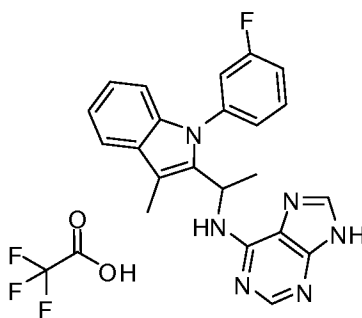
15

**Example 7. *N*-(1-(1-(3-Fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-9H-purin-6-amine bis(2,2,2-trifluoroacetate)**

A mixture of 1-[1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanamine (24 mg, 0.094 mmol), 6-bromo-9H-purine (29 mg, 0.14 mmol) and *N,N*-diisopropylethylamine (0.049 mL, 0.28 mmol) in ethanol (1 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5 μM; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a bis TFA salt. LCMS calculated for C<sub>20</sub>H<sub>17</sub>FN<sub>7</sub>(M+H)<sup>+</sup>: m/z = 374.2; Found: 374.1. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.16 (1H, br s), 8.46 (2H, m), 8.16 (1H, m), 8.04 (1H, m), 7.34 (2H, m), 7.16 (1H, m), 7.10 (1H, m), 6.79 (1H, s), 5.70 (1H, m), 1.62 (3H, d, *J* = 6.4 Hz) ppm. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 376 MHz) for the TFA salt: δ -75.1, -112.8 ppm.

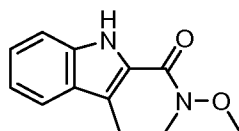
30

**Example 8. *N*-{1-[1-(3-Fluorophenyl)-3-methyl-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate**



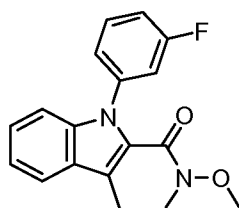
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*Step 1. N-Methoxy-N,3-dimethyl-1H-indole-2-carboxamide*



A mixture of 3-methyl-1H-indole-2-carboxylic acid (from Matrix Scientific,  
 10 1.0 g, 5.7 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium  
 hexafluorophosphate (4.3 g, 11 mmol) and triethylamine (4.0 mL, 28 mmol) in *N,N*-  
 dimethylformamide (20 mL) was stirred at room temperature for 10 minutes. *N,O*-  
 Dimethylhydroxylamine hydrochloride (0.84 g, 8.6 mmol) was added and the  
 resulting suspension was stirred at room temperature over the weekend. The mixture  
 15 was quenched with water and extracted with EtOAc. The combined organic layers  
 were dried over MgSO<sub>4</sub>, concentrated, and purified on silica gel (eluting with 0-30%  
 EtOAc/hexane) to give the desired product (1.1 g, 88%). LCMS calculated for  
 C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 219.1; Found: 219.1.

20 *Step 2. 1-(3-Fluorophenyl)-N-methoxy-N,3-dimethyl-1H-indole-2-*  
*carboxamide*

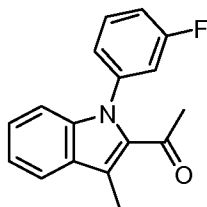


Activated molecular sieves (18 g) 4Å were placed in an oven dried flask and  
 cooled to room temperature under nitrogen. To the flask was charged with *N*-  
 25 methoxy-*N,3*-dimethyl-1H-indole-2-carboxamide (1.5 g, 6.9 mmol), (3-



fluorophenyl)boronic acid (2.9 g, 21 mmol), cupric acetate (1.9 g, 10 mmol), methylene chloride (130 mL) and pyridine (2.2 mL, 27 mmol). The reaction mixture  
5 was stirred at room temperature for 2 days. The mixture was filtered through a pad of Celite. The filtrate was concentrated and purified on silica gel (eluting with 0-30% EtOAc/hexane) to give the desired product (0.27 g, 12%). LCMS calculated for  $C_{18}H_{18}FN_2O_2(M+H)^+$ :  $m/z = 313.1$ ; Found: 313.0.

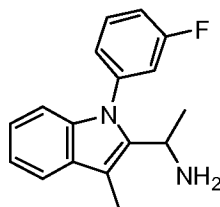
10 *Step 3. 1-[1-(3-Fluorophenyl)-3-methyl-1H-indol-2-yl]ethanone*



To a mixture of 1-(3-fluorophenyl)-*N*-methoxy-*N*,3-dimethyl-1H-indole-2-carboxamide (0.27 g, 0.86 mmol) in tetrahydrofuran (5 mL) was added 3.0 M methylmagnesium bromide in ether (2.3 mL, 6.9 mmol). The reaction was stirred at  
15 room temperature overnight. The reaction was quenched with saturated  $NH_4Cl$  solution and extracted with EtOAc. The combined organic layers were dried over  $MgSO_4$ , concentrated, and purified on silica gel (eluting with 0-15% EtOAc/hexane) to give the desired product (0.165 g, 71%). LCMS calculated for  $C_{17}H_{15}FNO(M+H)^+$ :  $m/z = 268.1$ ; Found: 268.0.

20

*Step 4. 1-[1-(3-Fluorophenyl)-3-methyl-1H-indol-2-yl]ethanamine*



A mixture of 1-[1-(3-fluorophenyl)-3-methyl-1H-indol-2-yl]ethanone (0.165 g, 0.617 mmol) and ammonium acetate (0.476 g, 6.17 mmol) in methanol (2.0 mL)  
25 and acetonitrile (2.0 mL) was heated at 65 °C in a sealed tube for 1 hour. After cooling to room temperature, sodium cyanoborohydride (0.12 g, 1.9 mmol) was added to the resultant mixture. The reaction was heated at 65 °C over the weekend. The reaction was cooled to room temperature and quenched with saturated  $NaHCO_3$  solution and then extracted with dichloromethane, dried over  $MgSO_4$  and

concentrated to give the crude amine (0.16 g), which was used directly in next step.  
LCMS calculated for  $C_{17}H_{18}FN_2(M+H)^+$ :  $m/z = 269.1$ ; Found: 252.1.

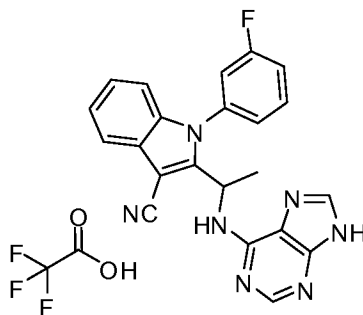
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*Step 5. N-{1-[1-(3-Fluorophenyl)-3-methyl-1H-indol-2-yl]ethyl}-9H-purin-6-amine trifluoroacetate*

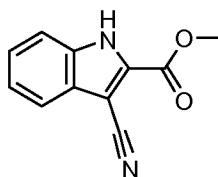
A mixture of 1-[1-(3-fluorophenyl)-3-methyl-1H-indol-2-yl]ethanamine (0.11 g, 0.41 mmol), 6-bromo-9H-purine (0.12 g, 0.61 mmol) and *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) in ethanol (2 mL) was heated at 110 °C overnight. The mixture was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5  $\mu$ M; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a TFA salt. LCMS calculated for  $C_{22}H_{20}FN_6(M+H)^+$ :  $m/z = 387.2$ ; Found: 387.1.  $^1H$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  8.98 (1H, br s), 8.39 (2H, m), 7.58 (1H, m), 7.49 (1H, m), 7.35 (1H, m), 7.30 (1H, m), 7.05 (2H, m), 6.88 (1H, m), 5.31 (1H, m), 2.36 (3H, s), 1.63 (3H, d,  $J = 6.0$  Hz) ppm.  $^{19}F$  NMR (DMSO- $d_6$ , 376 MHz) for the TFA salt:  $\delta$  -74.7, -111.9 ppm.

20

**Example 9. 2-(1-(9H-Purin-6-ylamino)ethyl)-1-(3-fluorophenyl)-1H-indole-3-carbonitrile 2,2,2-trifluoroacetate**



*Step 1. Methyl 3-cyano-1H-indole-2-carboxylate*

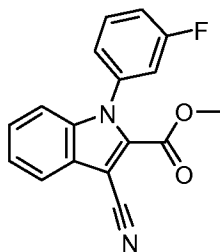


25

To a mixture of methyl 3-[(*E*)-(hydroxyimino)methyl]-1H-indole-2-carboxylate (from Key Organics, 1.0 g, 4.6 mmol) and pyridine (7.4 mL, 92 mmol) in

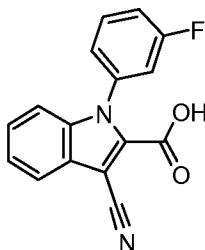
1,4-dioxane (20 mL) was added methanesulfonyl chloride (1.4 mL, 18 mmol). The reaction was heated at 60 °C for 2 hours. The reaction was diluted with water and  
5 extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, concentrated, and purified on silica gel (eluting with 0-5% MeOH/dichloromethane) to give the desired product (0.7 g, 76%). LCMS calculated for C<sub>11</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 201.1; Found: 201.1.

10 *Step 2. Methyl 3-cyano-1-(3-fluorophenyl)-1H-indole-2-carboxylate*



Activated molecular sieves (6.0 g, 27 mmol) 4Å were placed in an oven dried flask and cooled to room temperature under nitrogen. To the flask was charged with methyl 3-cyano-1H-indole-2-carboxylate (0.45 g, 2.2 mmol), (3-fluorophenyl)boronic  
15 acid (0.94 g, 6.7 mmol), cupric acetate (0.61 g, 3.4 mmol), methylene chloride (43 mL) and pyridine (0.73 mL, 9.0 mmol). The reaction mixture was stirred at room temperature over the weekend. The mixture was filtered through a pad of Celite. The filtrate was concentrated and purified on silica gel (eluting with 0-60% EtOAc/hexane) to give the desired product (0.39 g, 59%). LCMS calculated for  
20 C<sub>17</sub>H<sub>12</sub>FN<sub>2</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 295.1; Found: 295.0.

*Step 3. 3-Cyano-1-(3-fluorophenyl)-1H-indole-2-carboxylic acid*

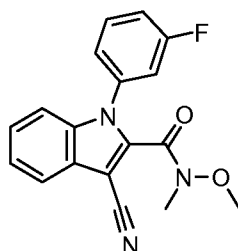


Methyl 3-cyano-1-(3-fluorophenyl)-1H-indole-2-carboxylate (0.13 g, 0.44  
25 mmol) was treated with 1.0 M lithium hydroxide in water (0.66 mL, 0.66 mmol) in methanol (3 mL) at room temperature for 3 hours. The reaction was diluted with 1 N HCl and extracted with EtOAc. The extracts were combined, washed with brine, dried

over  $\text{MgSO}_4$  and concentrated to give the desired acid (0.12 g, 97%). LCMS calculated for  $\text{C}_{16}\text{H}_{10}\text{FN}_2\text{O}_2(\text{M}+\text{H})^+$ :  $m/z = 281.1$ ; Found: 281.1.

5

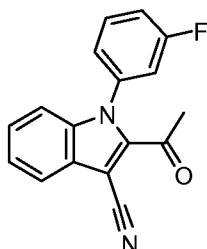
*Step 4. 3-Cyano-1-(3-fluorophenyl)-N-methoxy-N-methyl-1H-indole-2-carboxamide*



A mixture of 3-cyano-1-(3-fluorophenyl)-1H-indole-2-carboxylic acid (0.12 g, 0.43 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.32 g, 0.86 mmol) and *N,N*-diisopropylethylamine (0.37 mL, 2.1 mmol) in *N,N*-dimethylformamide (5 mL) was stirred at room temperature for 10 minutes. *N,O*-Dimethylhydroxylamine hydrochloride (63 mg, 0.64 mmol) was added and the resulting suspension was stirred at room temperature overnight. The mixture was quenched with water and extracted with EtOAc. The extracts were combined, dried over  $\text{MgSO}_4$ , concentrated, and purified on silica gel (eluting with 0-25% EtOAc/hexane) to give the desired product (90 mg, 65%). LCMS calculated for  $\text{C}_{18}\text{H}_{15}\text{FN}_3\text{O}_2(\text{M}+\text{H})^+$ :  $m/z = 324.1$ ; Found: 324.0.

20

*Step 5. 2-Acetyl-1-(3-fluorophenyl)-1H-indole-3-carbonitrile*



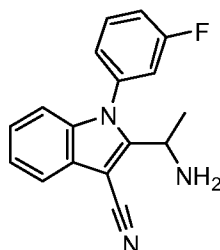
To a mixture of 3-cyano-1-(3-fluorophenyl)-*N*-methoxy-*N*-methyl-1H-indole-2-carboxamide (90 mg, 0.28 mmol) in tetrahydrofuran (3 mL) was added 3.0 M methylmagnesium bromide in ether (0.93 mL, 2.8 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$ , concentrated, and purified on silica gel (eluting with 0-15% EtOAc/hexane)

25

to give the desired product (43 mg, 56%). LCMS calculated for  $C_{17}H_{12}FN_2O(M+H)^+$ :  $m/z = 279.1$ ; Found: 279.0.

5

*Step 6. 2-(1-Aminoethyl)-1-(3-fluorophenyl)-1H-indole-3-carbonitrile*



A mixture of 2-acetyl-1-(3-fluorophenyl)-1H-indole-3-carbonitrile (43 mg, 0.15 mmol) and ammonium acetate (0.119 g, 1.54 mmol) in methanol (1.5 mL) and acetonitrile (1.5 mL) was heated at 65 °C in a sealed tube for 1 hour. After cooling to room temperature, sodium cyanoborohydride (29 mg, 0.46 mmol) was added to the resultant mixture. The reaction was heated at 65 °C overnight. The reaction was then cooled to room temperature, quenched with saturated  $NaHCO_3$  solution, and extracted with dichloromethane. The combined organic layers were dried over  $MgSO_4$  and concentrated to give the desired product (43 mg), which was used directly in the next step. LCMS calculated for  $C_{17}H_{15}FN_3(M+H)^+$ :  $m/z = 280.1$ ; Found: 280.1.

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*Step 7. 2-(1-(9H-Purin-6-ylamino)ethyl)-1-(3-fluorophenyl)-1H-indole-3-carbonitrile 2,2,2-trifluoroacetate*

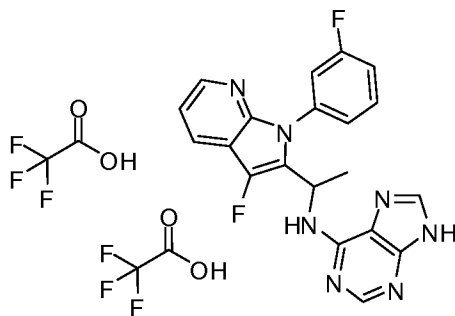
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A mixture of 2-(1-aminoethyl)-1-(3-fluorophenyl)-1H-indole-3-carbonitrile (4.0 mg, 0.014 mmol), 6-bromo-9H-purine (4.3 mg, 0.021 mmol) and *N,N*-diisopropylethylamine (7.5  $\mu$ L, 0.043 mmol) in ethanol (0.6 mL) was heated at 110 °C overnight. The mixture was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5  $\mu$ M; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a TFA salt. LCMS calculated for  $C_{22}H_{17}FN_7(M+H)^+$ :  $m/z = 398.2$ ; Found: 397.9.  $^1H$  NMR ( $DMSO-d_6$ , 400 MHz)  $\delta$  8.79 (1H, br s), 8.33 (1H, m), 8.28 (1H, m), 7.41 (1H, m), 7.38 (1H, m), 7.32 (1H, m), 7.27 (1H, m), 7.22 (2H, m), 7.11 (1H, m), 6.93 (1H, m), 5.50 (1H, m), 1.71 (3H, d,  $J = 6.6$  Hz) ppm.  $^{19}F$  NMR ( $DMSO-d_6$ , 376 MHz) for the TFA salt:  $\delta$  -74.7, -112.7 ppm.

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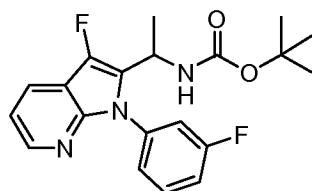
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**Example 10. *N*-(1-(3-Fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-9H-purin-6-amine bis(2,2,2-trifluoroacetate)**



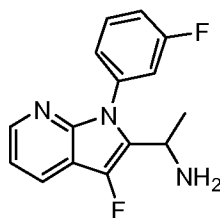
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*Step 1. tert-Butyl {1-[3-fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}carbamate*



10 A mixture of *tert*-butyl {1-[1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}carbamate (0.10 g, 0.28 mmol) and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (0.10 g, 0.28 mmol) in acetonitrile (1.5 mL, 29 mmol) and water (0.15 mL, 8.3 mmol) was heated at 50 °C overnight. The reaction was cooled and extracted with dichloromethane. The combined organic  
15 layers were dried over MgSO<sub>4</sub>, concentrated and purified on silica gel (eluting with 0-20% EtOAc/hexane) to give the desired product (16 mg, 15%). LCMS calculated for C<sub>20</sub>H<sub>22</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub>(M+H)<sup>+</sup>: m/z = 374.2; Found: 374.1.

20 *Step 2. 1-[3-Fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanamine*



To a mixture of *tert*-butyl {1-[3-fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}carbamate (16 mg, 0.043 mmol) in methylene chloride (1 mL)

was added trifluoroacetic acid (0.033 mL, 0.43 mmol). The reaction was stirred at room temperature for 1 hour. The reaction was quenched with saturated NaHCO<sub>3</sub> solution and then extracted with dichloromethane. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated to give the desired amine (11 mg, 94%). LCMS calculated for C<sub>15</sub>H<sub>14</sub>F<sub>2</sub>N<sub>3</sub>(M+H)<sup>+</sup>: m/z = 274.1; Found: 274.1.

*Step 3. N-(1-(3-Fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-9H-purin-6-amine bis(2,2,2-trifluoroacetate)*

A mixture of 1-[3-fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethanamine (11 mg, 0.040 mmol), 6-bromo-9H-purine (9.6 mg, 0.048 mmol) and *N,N*-diisopropylethylamine (0.018 mL, 0.10 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was purified on preparative-LCMS (XBridge C18 column, 19x100 mm, 5 μM; eluting with a gradient of acetonitrile/water containing 01.% TFA; at flow rate 30 mL/min; with injection volume of 2 mL) to give the desired product as a bis TFA salt. LCMS calculated for C<sub>20</sub>H<sub>16</sub>F<sub>2</sub>N<sub>7</sub>(M+H)<sup>+</sup>: m/z = 392.1; Found: 392.0.

#### **Example A: PI3Kδ scintillation proximity assay**

##### Materials

[γ-<sup>33</sup>P]ATP (10mCi/mL) was purchased from Perkin–Elmer (Waltham, MA). Lipid kinase substrate, D-myo-Phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P<sub>2</sub>)D (+)-sn-1,2-di-O-octanoylglyceryl, 3-O-phospho linked (PIP<sub>2</sub>), CAS 204858-53-7, was purchased from Echelon Biosciences (Salt Lake City, UT). PI3Kδ (p110δ /p85α) was purchased from Millipore (Bedford, MA). ATP, MgCl<sub>2</sub>, DTT, EDTA, MOPS and CHAPS were purchased from Sigma–Aldrich (St. Louis, MO). Wheat Germ Agglutinin (WGA) YSi SPA Scintillation Beads was purchased from GE healthcare life sciences (Piscataway, NJ).

The kinase reaction was conducted in polystyrene 384-well matrix white plate from Thermo Fisher Scientific in a final volume of 25 μL. Inhibitors were first diluted serially in DMSO and added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 0.5%. The PI3K assays were carried out at room temperature in 20 mM MOPS, pH 6.7, 10 mM MgCl<sub>2</sub>, 5 mM DTT and CHAPS 0.03%. Reactions were initiated by the addition of ATP, the final reaction mixture consisted of 20 μM PIP<sub>2</sub>, 20 μM ATP, 0.2 μCi [γ-<sup>33</sup>P]

ATP, 4 nM PI3K $\delta$ . Reactions were incubated for 210 min and terminated by the addition of 40  $\mu$ L SPA beads suspended in quench buffer: 150mM potassium phosphate pH 8.0, 20% glycerol, 25 mM EDTA, 400  $\mu$ M ATP. The final concentration of SPA beads was 1.0mg/mL. After the plate sealing, plates were shaken overnight at room temperature and centrifuged at 1800 rpm for 10 minutes, the radioactivity of the product was determined by scintillation counting on Topcount (Perkin–Elmer). IC<sub>50</sub> determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the GraphPad Prism 3.0 software. See Table 1 for data related to compounds of the invention (TFA salts of racemates of each of the compounds were tested).

**Table 1**

Example	PI3K $\delta$ IC <sub>50</sub> (nM)*
1	+++
2	+
3	+
4	++
5	++
6	+
7	++++
8	+
9	+
10	+++

15

\*50 nM or less (+); >50 nM to 100 nM (++); >100 nM to 250 nM (+++); >250 nM to 750 nM (++++); and >1000 nM (+++++)

**Example B: B cell proliferation assay**

To acquire B cells, human PBMC are isolated from the peripheral blood of normal, drug free donors by standard density gradient centrifugation on Ficoll-Hypaque (GE Healthcare, Piscataway, NJ) and incubated with anti-CD19 microbeads (Miltenyi Biotech, Auburn, CA). The B cells are then purified by positive immunosorting using an autoMacs (Miltenyi Biotech) according to the manufacture's instruction.

25

The purified B cells ( $2 \times 10^5$ /well/200  $\mu$ L) are cultured in 96-well ultra-low binding plates (Corning, Corning, NY) in RPMI1640, 10% FBS and goat F(ab')<sub>2</sub> anti-human IgM (10  $\mu$ g/ml) (Invitrogen, Carlsbad, CA), in the presence of different



amount of test compounds, for three days. [<sup>3</sup>H]-thymidine (1 μCi/well) (PerkinElmer, Boston, MA) in PBS is then added to the B cell cultures for an additional 12 hours  
5 before the incorporated radioactivity are separated by filtration with water through GF/B filters (Packard Bioscience, Meriden, CT) and measured by liquid scintillation counting with a TopCount (Packard Bioscience).

**Example C: Pfeiffer cell proliferation assay**

10 Pfeiffer cell line (diffuse large B cell lymphoma) is purchased from ATCC (Manassas, VA) and maintained in the culture medium recommended (RPMI and 10% FBS). To measure the anti-proliferation activity of the PI3Kδ submittals, the Pfeiffer cells are plated with the culture medium (2x10<sup>3</sup> cells / well/ per 200 μl) into 96-well ultra-low binding plates (Corning, Corning, NY), in the presence or absence  
15 of a concentration range of test compounds. After 3-4 days, [<sup>3</sup>H]-thymidine (1 μCi/well) (PerkinElmer, Boston, MA) in PBS is then added to the cell culture for an additional 12 hrs before the incorporated radioactivity was separated by filtration with water through GF/B filters (Packard Bioscience, Meridenj, CT) and measured by liquid scintillation counting with a TopCount (Packard Bioscience).

20 **Example D: Akt phosphorylation assay**

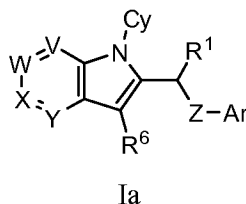
Ramos cells (B lymphocyte from Burkitts lymphoma) are obtained from ATCC (Manassas, VA) and maintained in RPMI1640 and 10% FBS. The cells (3x10<sup>7</sup> cells /tube/3 mL in RPMI) are incubated with different amounts of test  
25 compounds for 2 hours at 37 °C and then stimulated with goat F(ab')<sub>2</sub> anti-human IgM (5 μg/mL) (Invitrogen) for 17 minutes. in a 37 °C water bath. The stimulated cells are spun down at 4 °C with centrifugation and whole cell extracts are prepared using 300 μL lysis buffer (Cell Signaling Technology, Danvers, MA). The resulting lysates are sonicated and supernatants are collected. The phosphorylation level of Akt  
30 in the supernatants are analyzed by using PathScan phospho-Akt1 (Ser473) sandwich ELISA kits (Cell Signaling Technology) according to the manufacture's instruction.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each

reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

## WHAT IS CLAIMED IS:

1. The compound of claim 1, having Formula Ia:



or a pharmaceutically acceptable salt thereof; wherein:

V is CR<sup>2</sup> or N;

W is CR<sup>3</sup> or N;

X is CR<sup>4</sup> or N;

Y is CR<sup>5</sup> or N;

provided that -V=W-X=Y- is selected from -CR<sup>2</sup>=CR<sup>3</sup>-CR<sup>4</sup>=CR<sup>5</sup>-, -N=CR<sup>3</sup>-CR<sup>4</sup>=CR<sup>5</sup>-, -CR<sup>2</sup>=N-CR<sup>4</sup>=CR<sup>5</sup>-, -CR<sup>2</sup>=CR<sup>3</sup>-N=CR<sup>5</sup>-, and -CR<sup>2</sup>=CR<sup>3</sup>-CR<sup>4</sup>=N-;

Z is O, S, or NR<sup>A</sup>;

provided that when R<sup>6</sup> is bromo or -CO<sub>2</sub>(ethyl), then Z is O or NR<sup>A</sup>;

Cy is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups;

each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO<sub>2</sub>, OR<sup>a</sup>, SR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, C(=NR<sup>c</sup>)R<sup>b</sup>, C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(=NR<sup>c</sup>)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>S(O)R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halosulfanyl, CN, NO<sub>2</sub>, OR<sup>a2</sup>, SR<sup>a2</sup>, C(O)R<sup>b2</sup>, C(O)NR<sup>c2</sup>R<sup>d2</sup>, C(O)OR<sup>a2</sup>, OC(O)R<sup>b2</sup>, OC(O)NR<sup>c2</sup>R<sup>d2</sup>, C(=NR<sup>g</sup>)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>C(=NR<sup>g</sup>)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>C(O)R<sup>b2</sup>, NR<sup>c2</sup>C(O)OR<sup>a2</sup>, NR<sup>c2</sup>C(O)NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>S(O)R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>NR<sup>c2</sup>R<sup>d2</sup>, S(O)R<sup>b2</sup>, S(O)NR<sup>c2</sup>R<sup>d2</sup>, S(O)<sub>2</sub>R<sup>b2</sup>, and S(O)<sub>2</sub>NR<sup>c2</sup>R<sup>d2</sup>;

R<sup>1</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl, and C<sub>2-6</sub> alkynyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, and C<sub>2-6</sub> alkynyl are each

optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo, OH, CN,  $\text{NR}^{1a}\text{R}^{2b}$ ,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  haloalkoxy, thio,  $\text{C}_{1-6}$  alkylthio,  $\text{C}_{1-6}$  alkylsulfinyl,  $\text{C}_{1-6}$  alkylsulfonyl, carbamyl,  $\text{C}_{1-6}$  alkylcarbamyl,  $\text{di}(\text{C}_{1-6}$  alkyl)carbamyl, carboxy,  $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy carbonyl,  $\text{C}_{1-6}$  alkylcarbonylamino,  $\text{C}_{1-6}$  alkylsulfonylamino, aminosulfonyl,  $\text{C}_{1-6}$  alkylaminosulfonyl,  $\text{di}(\text{C}_{1-6}$  alkyl)aminosulfonyl, aminosulfonylamino,  $\text{C}_{1-6}$  alkylaminosulfonylamino,  $\text{di}(\text{C}_{1-6}$  alkyl)aminosulfonylamino, aminocarbonylamino,  $\text{C}_{1-6}$  alkylaminocarbonylamino, and  $\text{di}(\text{C}_{1-6}$  alkyl)aminocarbonylamino;

each  $\text{R}^{1a}$  and  $\text{R}^{2b}$  is independently selected from H and  $\text{C}_{1-6}$  alkyl;

or any  $\text{R}^{1a}$  and  $\text{R}^{2b}$  together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group, which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $\text{C}_{1-6}$  alkyl;

$\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ , and  $\text{R}^6$  are each independently selected from H, OH,  $\text{NO}_2$ , CN, halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{1-6}$  haloalkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  haloalkoxy, amino,  $\text{C}_{1-6}$  alkylamino,  $\text{di}(\text{C}_{1-6}$  alkyl)amino, thio,  $\text{C}_{1-6}$  alkylthio,  $\text{C}_{1-6}$  alkylsulfinyl,  $\text{C}_{1-6}$  alkylsulfonyl, carbamyl,  $\text{C}_{1-6}$  alkylcarbamyl,  $\text{di}(\text{C}_{1-6}$  alkyl)carbamyl, carboxy,  $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy carbonyl,  $\text{C}_{1-6}$  alkylcarbonylamino,  $\text{C}_{1-6}$  alkylsulfonylamino, aminosulfonyl,  $\text{C}_{1-6}$  alkylaminosulfonyl,  $\text{di}(\text{C}_{1-6}$  alkyl)aminosulfonyl, aminosulfonylamino,  $\text{C}_{1-6}$  alkylaminosulfonylamino,  $\text{di}(\text{C}_{1-6}$  alkyl)aminosulfonylamino, aminocarbonylamino,  $\text{C}_{1-6}$  alkylaminocarbonylamino, and  $\text{di}(\text{C}_{1-6}$  alkyl)aminocarbonylamino;

Ar is bicyclic azaheteroaryl, substituted with n independently selected  $\text{R}^D$  groups; wherein n is 0, 1, 2, 3, 4, or 5;

each  $\text{R}^D$  is independently selected from  $-(\text{C}_{1-4}$  alkyl)<sub>r</sub>- $\text{Cy}^1$ , halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{1-6}$  haloalkyl, halosulfonyl, CN,  $\text{NO}_2$ ,  $\text{OR}^{a1}$ ,  $\text{SR}^{a1}$ ,  $\text{C}(\text{O})\text{R}^{b1}$ ,  $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{C}(\text{O})\text{OR}^{a1}$ ,  $\text{OC}(\text{O})\text{R}^{b1}$ ,  $\text{OC}(\text{O})\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{NR}^{c1}\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{NR}^{c1}\text{C}(\text{O})\text{R}^{b1}$ ,  $\text{NR}^{c1}\text{C}(\text{O})\text{OR}^{a1}$ ,  $\text{NR}^{c1}\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{NR}^{c1}\text{S}(\text{O})\text{R}^{b1}$ ,  $\text{NR}^{c1}\text{S}(\text{O})_2\text{R}^{b1}$ ,  $\text{NR}^{c1}\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{S}(\text{O})\text{R}^{b1}$ ,  $\text{S}(\text{O})\text{NR}^{c1}\text{R}^{d1}$ ,  $\text{S}(\text{O})_2\text{R}^{b1}$ , and  $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$ ;

$\text{R}^A$  is selected from H,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl, and  $\text{C}_{2-6}$  alkynyl;

each  $\text{Cy}^1$  is, independently, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from OH,  $\text{NO}_2$ , CN, halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{1-6}$  haloalkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  haloalkoxy, amino,  $\text{C}_{1-6}$  alkylamino,  $\text{di}(\text{C}_{1-6}$  alkyl)amino, thio,  $\text{C}_{1-6}$  alkylthio,  $\text{C}_{1-6}$

alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>a</sup>, R<sup>c</sup>, and R<sup>d</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>b</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

or any R<sup>c</sup> and R<sup>d</sup> together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>c</sup> and R<sup>g</sup> is independently selected from H, C<sub>1-6</sub> alkyl, and CN;

each R<sup>al</sup>, R<sup>cl</sup>, and R<sup>dl</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>bl</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl,

carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

or any R<sup>c1</sup> and R<sup>d1</sup> together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>a2</sup>, R<sup>c2</sup>, and R<sup>d2</sup> is independently selected from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

each R<sup>b2</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,

cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino;

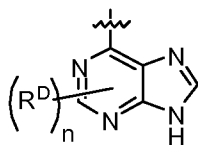
or any R<sup>c2</sup> and R<sup>d2</sup> together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO<sub>2</sub>, CN, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub> alkyl)amino, thio, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, carboxy, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulfonylamino, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl, di(C<sub>1-6</sub> alkyl)aminosulfonyl, aminosulfonylamino, C<sub>1-6</sub> alkylaminosulfonylamino, di(C<sub>1-6</sub> alkyl)aminosulfonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, and di(C<sub>1-6</sub> alkyl)aminocarbonylamino; and

r is 0 or 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z is NR<sup>A</sup>.
3. The compound of any one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, wherein Cy is aryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups.
4. The compound of any one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, wherein Cy is heterocycloalkyl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups.



5. The compound of any one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, wherein Cy is monocyclic heterocycloalkyl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups.
6. The compound of any one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, wherein Cy is heteroaryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups.
7. The compound of any one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, wherein Cy is monocyclic heteroaryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups.
8. The compound of any one of claims 1 to 2, or a pharmaceutically acceptable salt thereof, wherein Cy is a phenyl ring, which is optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups.
9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, CN, NO<sub>2</sub>, OR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>; wherein said C<sub>1-6</sub> alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy, C<sub>1-6</sub> alkoxy, and C<sub>1-6</sub> haloalkoxy.
10. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein each R<sup>C</sup> is independently halo.
11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein Ar is a purine ring, substituted with n independently selected R<sup>D</sup> groups; wherein n is 0, 1, or 2.
12. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein Ar is a moiety of formula:



wherein n is 0 or 1.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein n is 0.
14. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein each  $R^D$  is, independently,  $NR^{c1}R^{d1}$ .
15. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein each  $R^D$  is independently selected from amino,  $C_{1-6}$  alkylamino, and di( $C_{1-6}$ -alkyl)amino.
16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is selected from  $C_{1-6}$  alkyl.
17. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is methyl.
18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein  $R^A$  is H.
19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are independently selected from H, CN, halo,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkoxy, and  $C_{1-6}$  haloalkoxy.
20. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are independently selected from H, CN, halo, and  $C_{1-6}$  alkyl.

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is H, CN, F, Cl, or methyl.
22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein V is  $CR^2$ .
23. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein V is N.
24. The compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein W is  $CR^3$ .
25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein X is  $CR^4$ .
26. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein Y is  $CR^5$ .
27. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- Z is NH;
  - Cy is heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected  $R^C$  groups;
  - each  $R^C$  is independently selected from halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halosulfanyl, CN,  $NO_2$ ,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cC(O)NR^cR^d$ ,  $C(=NR^e)R^b$ ,  $C(=NR^e)NR^cR^d$ ,  $NR^cC(=NR^e)NR^cR^d$ ,  $NR^cS(O)R^b$ ,  $NR^cS(O)_2R^b$ ,  $NR^cS(O)_2NR^cR^d$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ;
- wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halosulfanyl, CN,  $NO_2$ ,  $OR^{a2}$ ,  $SR^{a2}$ ,  $C(O)R^{b2}$ ,  $C(O)NR^{c2}R^{d2}$ ,  $C(O)OR^{a2}$ ,  $OC(O)R^{b2}$ ,  $OC(O)NR^{c2}R^{d2}$ ,  $C(=NR^g)NR^{c2}R^{d2}$ ,  $NR^{c2}C(=NR^g)NR^{c2}R^{d2}$ ,  $NR^{c2}R^{d2}$ ,  $NR^{c2}C(O)R^{b2}$ ,  $NR^{c2}C(O)OR^{a2}$ ,

$\text{NR}^{\text{c}2}\text{C}(\text{O})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$ ,  $\text{NR}^{\text{c}2}\text{S}(\text{O})\text{R}^{\text{b}2}$ ,  $\text{NR}^{\text{c}2}\text{S}(\text{O})_2\text{R}^{\text{b}2}$ ,  $\text{NR}^{\text{c}2}\text{S}(\text{O})_2\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$ ,  $\text{S}(\text{O})\text{R}^{\text{b}2}$ ,  $\text{S}(\text{O})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$ ,  $\text{S}(\text{O})_2\text{R}^{\text{b}2}$ , and  $\text{S}(\text{O})_2\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$ ;

Ar is a bicyclic azaheteroaryl group, substituted with n independently selected  $\text{R}^{\text{D}}$  groups; wherein n is 0, 1, 2, 3, or 4;

each  $\text{R}^{\text{D}}$  is, independently,  $\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$ ;

$\text{R}^1$  is, independently,  $\text{C}_{1-6}$  alkyl;

$\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ , and  $\text{R}^5$  are independently selected from H, OH, CN, halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C}_{1-4}$  haloalkoxy, amino,  $\text{C}_{1-4}$  alkylamino, di( $\text{C}_{1-4}$ -alkyl)amino, carboxy,  $\text{C}_{1-4}$  alkylcarbonyl,  $\text{C}_{1-4}$  alkoxy carbonyl, carbamyl,  $\text{C}_{1-4}$  alkylcarbamyl, di( $\text{C}_{1-4}$ -alkyl)carbamyl,  $\text{C}_{1-4}$  alkylcarbonylamino,  $\text{C}_{1-4}$  alkylthio,  $\text{C}_{1-4}$  alkylsulfinyl, and  $\text{C}_{1-4}$  alkylsulfonyl; and

$\text{R}^6$  is H, CN, halo, or  $\text{C}_{1-6}$  alkyl.

28. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Z is NH;

Cy is heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected  $\text{R}^{\text{C}}$  groups;

each  $\text{R}^{\text{C}}$  is independently selected from halo,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{1-6}$  haloalkyl, CN,  $\text{NO}_2$ ,  $\text{OR}^{\text{a}}$ ,  $\text{C}(\text{O})\text{R}^{\text{b}}$ ,  $\text{C}(\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ,  $\text{C}(\text{O})\text{OR}^{\text{a}}$ ,  $\text{OC}(\text{O})\text{R}^{\text{b}}$ ,  $\text{OC}(\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ,  $\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ,  $\text{NR}^{\text{c}}\text{C}(\text{O})\text{R}^{\text{b}}$ ,  $\text{NR}^{\text{c}}\text{C}(\text{O})\text{OR}^{\text{a}}$ ,  $\text{NR}^{\text{c}}\text{C}(\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ,  $\text{S}(\text{O})\text{R}^{\text{b}}$ ,  $\text{S}(\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ,  $\text{S}(\text{O})_2\text{R}^{\text{b}}$ , and  $\text{S}(\text{O})_2\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ; wherein said  $\text{C}_{1-6}$  alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy,  $\text{C}_{1-6}$  alkoxy, and  $\text{C}_{1-6}$  haloalkoxy;

Ar is a purine ring, substituted with n independently selected  $\text{R}^{\text{D}}$  groups; wherein n is 0 or 1;

each  $\text{R}^{\text{D}}$  is, independently,  $\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$ ;

$\text{R}^1$  is  $\text{C}_{1-6}$  alkyl;

$\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ , and  $\text{R}^5$  are each independently selected from H, halo, CN,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  haloalkyl,  $\text{C}_{1-6}$  alkoxy, and  $\text{C}_{1-6}$  haloalkoxy; and

$\text{R}^6$  is H, CN, halo, or  $\text{C}_{1-6}$  alkyl.

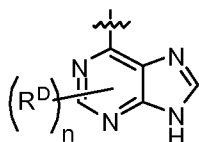
29. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Z is NH;

Cy is heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups;

each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, CN, NO<sub>2</sub>, OR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>; wherein said C<sub>1-6</sub> alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy, C<sub>1-6</sub> alkoxy, and C<sub>1-6</sub> haloalkoxy;

Ar is a moiety of formula:



wherein n is 0 or 1;

each R<sup>D</sup> is, independently, NR<sup>c1</sup>R<sup>d1</sup>;

R<sup>1</sup> is C<sub>1-6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are each independently selected from H, halo, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, and C<sub>1-6</sub> haloalkoxy; and

R<sup>6</sup> is H, CN, halo, or C<sub>1-6</sub> alkyl.

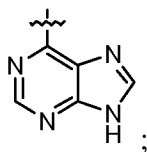
30. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Z is NH;

Cy is heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted with 1, 2, 3, 4, or 5 independently selected R<sup>C</sup> groups;

each R<sup>C</sup> is independently selected from halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, CN, NO<sub>2</sub>, OR<sup>a</sup>, C(O)R<sup>b</sup>, C(O)NR<sup>c</sup>R<sup>d</sup>, C(O)OR<sup>a</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>R<sup>d</sup>, NR<sup>c</sup>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>R<sup>d</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>c</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>; wherein said C<sub>1-6</sub> alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from hydroxy, C<sub>1-6</sub> alkoxy, and C<sub>1-6</sub> haloalkoxy;

Ar is a moiety of formula:



$R^1$  is  $C_{1-6}$  alkyl;

$R^2$ ,  $R^3$ ,  $R^4$ , and  $R^5$  are each independently selected from H, halo, CN,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkoxy, and  $C_{1-6}$  haloalkoxy; and

$R^6$  is H, CN, halo, or  $C_{1-6}$  alkyl.

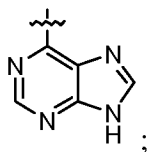
31. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Z is NH;

Cy is aryl, optionally substituted with 1, 2, 3, 4, or 5 independently selected  $R^C$  groups;

each  $R^C$  is independently selected from halo;

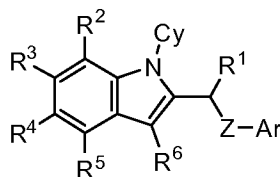
Ar is a moiety of formula:



$R^1$  is  $C_{1-6}$  alkyl; and

$R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are each independently selected from H, halo, CN,  $C_{1-6}$  alkyl, and  $C_{1-6}$  haloalkyl.

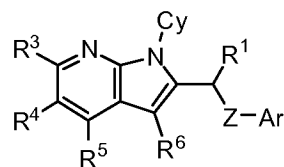
32. The compound of any one of claims 1 to 21 and 27 to 31, having Formula II:



II

or a pharmaceutically acceptable salt thereof.

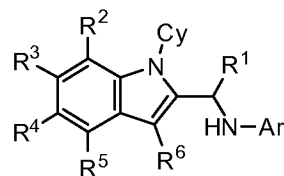
33. The compound of any one of claims 1 to 21 and 27 to 31, having Formula III:



III

or a pharmaceutically acceptable salt thereof.

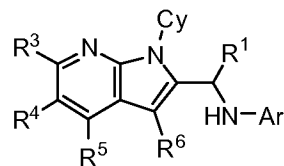
34. The compound of any one of claims 1 to 21 and 27 to 31, having Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

35. The compound of any one of claims 1 to 21 and 27 to 31, having Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof.

36. The compound according to claim 1, selected from:

*N*-{1-[6-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;

*N*-{1-[4-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;

*N*-{1-[3-chloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;

*N*-{1-[3,4-dichloro-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;

*N*-{1-[3-bromo-1-(3-fluorophenyl)-1H-indol-2-yl]ethyl}-9H-purin-6-amine;

*N*-{1-[3-chloro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]ethyl}-9H-purin-6-amine;

*N*-(1-(1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-9H-purin-6-amine;

*N*-{1-[1-(3-fluorophenyl)-3-methyl-1H-indol-2-yl]ethyl}-9H-purin-6-amine;

2-(1-(9H-purin-6-ylamino)ethyl)-1-(3-fluorophenyl)-1H-indole-3-carbonitrile;  
and  
N-(1-(3-fluoro-1-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)-9H-purin-6-amine;  
or a pharmaceutically acceptable salt of any of the aforementioned.

37. A composition comprising a compound according to any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

38. A method of modulating an activity of a PI3K kinase, comprising contacting the kinase with a compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof.

39. The method of claim 38, wherein the PI3K is selected from the group consisting of PI3K $\alpha$ , PI3K $\beta$ , PI3K $\gamma$ , and PI3K $\delta$ .

40. The method of claim 38, wherein said PI3K comprises a mutation.

41. The method of any one of claims 38 to 40, wherein said modulating is inhibiting.

42. The method of any one of claims 38 to 40, wherein said compound is a selective inhibitor for PI3K $\delta$  over one or more of PI3K $\alpha$ , PI3K $\beta$ , and PI3K $\gamma$ .

43. A method of treating a disease in a patient, wherein said disease is associated with abnormal expression or activity of a PI3K kinase, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof.

44. The method of claim 43, wherein said disease is osteoarthritis, restenosis, atherosclerosis, bone disorders, arthritis, diabetic retinopathy, psoriasis, benign prostatic hypertrophy, inflammation, angiogenesis, pancreatitis, kidney disease,



inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or Sjögren's syndrome.

45. The method of any one of claims 43 to 44, wherein more than one of said compounds is administered.

46. The method of claim 45, wherein the compound is administered in combination with a kinase inhibitor that inhibits a kinase other than a PI3K kinase.

47. A method of treating an immune-based disease in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof.

48. The method of claim 47, wherein said immune-based disease is rheumatoid arthritis, allergy, asthma, glomerulonephritis, lupus, or inflammation related to any of the aforementioned.

49. A method of treating a cancer in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claim 1 to 36, or a pharmaceutically acceptable salt thereof.

50. The method of claim 49, wherein said cancer is breast, prostate, colon, endometrial, brain, bladder, skin, uterus, ovary, lung, pancreatic, renal, gastric, or a hematological cancer.

51. The method of claim 50, wherein said hematological cancer is acute myeloblastic leukemia, chronic myeloid leukemia, or B cell lymphoma.

52. A method of treating a lung disease in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof.

53. The method of claim 52, wherein said lung disease is acute lung injury (ALI) or adult respiratory distress syndrome (ARDS).

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2011/041202

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C07D473/34 C07D519/00 A61K31/52 A61P35/00  
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
 EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 21 39 107 A1 (MERCK PATENT GMBH) 15 February 1973 (1973-02-15) claims; example 3	1-53
A	----- US 2005/261317 A1 (SADHU ET. AL.) 23 November 2005 (2005-11-23) page 3, line 21 - line 23; claims; examples	1-53
A	----- WO 2005/113556 A1 (ICOS CORPORATION) 1 December 2005 (2005-12-01) page 8, line 29 - page 10, line 3; claims; examples	1-53
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Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search  2 September 2011	Date of mailing of the international search report  23/09/2011
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Helps, Ian
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2011/041202

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/057048 A1 (CALISTOGA PHARMACEUTICALS INC.) 20 May 2010 (2010-05-20) page 1, paragraph 3 - page 2, paragraph 8; claims; examples -----	1-53
X,P	WO 2010/114900 A1 (ARQULE INC.) 7 October 2010 (2010-10-07) page 1, paragraph 2 - page 2, paragraph 7; claims; examples -----	1-53
E	WO 2011/075643 A1 (INCYTE CORPORATION) 23 June 2011 (2011-06-23) page 1 - page 3; claims; examples -----	1-53

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2011/041202
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			US 2010152211 A1 17-06-2010
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			US 2010256168 A1 07-10-2010
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