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**Vechorkin et al.**(10) **Pub. No.: US 2018/0072741 A1**(43) **Pub. Date: Mar. 15, 2018**(54) **PYRAZOLOPYRIMIDINE COMPOUNDS AND  
USES THEREOF****Related U.S. Application Data**(60) Provisional application No. 62/385,604, filed on Sep.  
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**Hummel**, Hockessin, DE (US)(51) **Int. Cl.**  
**C07D 487/04** (2006.01)(52) **U.S. Cl.**  
CPC ..... **C07D 487/04** (2013.01)(57) **ABSTRACT**

Disclosed are compounds of Formula (I), methods of using the compounds for inhibiting HPK1 activity and pharmaceutical compositions comprising such compounds. The compounds are useful in treating, preventing or ameliorating diseases or disorders associated with HPK1 activity such as cancer.

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# PYRAZOLOPYRIMIDINE COMPOUNDS AND USES THEREOF

## FIELD OF THE INVENTION

[0001] The disclosure provides compounds as well as their compositions and methods of use. The compounds modulate hematopoietic progenitor kinase 1 (HPK1) activity and are useful in the treatment of various diseases including cancer.

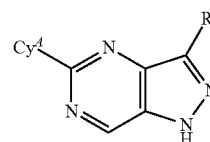
## BACKGROUND OF THE INVENTION

[0002] Hematopoietic progenitor kinase 1 (HPK1) originally cloned from hematopoietic progenitor cells is a member of MAP kinase kinase kinase kinases (MAP4Ks) family, which includes MAP4K1/HPK1, MAP4K2/GCK, MAP4K3/GLK, MAP4K4/HGK, MAP4K5/KHS, and MAP4K6/MINK (Hu, M. C., et al., *Genes Dev*, 1996, 10(18): p. 2251-64). HPK1 is of particular interest because it is predominantly expressed in hematopoietic cells such as T cells, B cells, macrophages, dendritic cells, neutrophils, and mast cells (Hu, M. C., et al., *Genes Dev*, 1996, 10(18): p. 2251-64; Kiefer, F., et al., *EMBO J*, 1996, 15(24): p. 7013-25). HPK1 kinase activity has been shown to be induced upon activation of T cell receptors (TCR) (Liou, J., et al., *Immunity*, 2000, 12(4): p. 399-408), B cell receptors (BCR) (Liou, J., et al., *Immunity*, 2000, 12(4): p. 399-408), transforming growth factor receptor (TGF- $\beta$ R) (Wang, W., et al., *J Biol Chem*, 1997, 272(36): p. 22771-5; Zhou, G., et al., *J Biol Chem*, 1999, 274(19): p. 13133-8), or  $G_s$ -coupled PGE<sub>2</sub> receptors (EP2 and EP4) (Ikegami, R., et al., *J Immunol*, 2001, 166(7): p. 4689-96). As such, HPK1 regulates diverse functions of various immune cells.

[0003] HPK1 is important in regulating the functions of various immune cells and it has been implicated in autoimmune diseases and anti-tumor immunity (Shui, J. W., et al., *Nat Immunol*, 2007, 8(1): p. 84-91; Wang, X., et al., *J Biol Chem*, 2012, 287(14): p. 11037-48). HPK1 knockout mice were more susceptible to the induction of experimental autoimmune encephalomyelitis (EAE) (Shui, J. W., et al., *Nat Immunol*, 2007, 8(1): p. 84-91). In human, HPK1 was downregulated in peripheral blood mononuclear cells of psoriatic arthritis patients or T cells of systemic lupus erythematosus (SLE) patients (Batliwalla, F. M., et al., *Mol Med*, 2005, 11(1-12): p. 21-9). Those observations suggested that attenuation of HPK1 activity may contribute to autoimmunity in patients. Furthermore, HPK1 may also control anti-tumor immunity via T cell-dependent mechanisms. In the PGE<sub>2</sub>-producing Lewis lung carcinoma tumor model, the tumors developed more slowly in HPK1 knockout mice as compared to wild-type mice (see US 2007/0087988). In addition, it was shown that adoptive transfer of HPK1 deficient T cells was more effective in controlling tumor growth and metastasis than wild-type T cells (Alzabin, S., et al., *Cancer Immunol Immunother*, 2010, 59(3): p. 419-29). Similarly, BMDCs from HPK1 knockout mice were more efficient to mount a T cell response to eradicate Lewis lung carcinoma as compared to wild-type BMDCs (Alzabin, S., et al., *J Immunol*, 2009, 182(10): p. 6187-94). These data, in conjunction with the restricted expression of HPK1 in hematopoietic cells and lack of effect on the normal development of immune cells, suggest that HPK1 may be an excellent drug target for enhancing antitumor immunity. Accordingly, there is a need for new compounds that modulate HPK1 activity.

## SUMMARY

[0004] The present disclosure provides, inter alia, a compound of Formula (I):



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

[0005] The present disclosure further provides a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

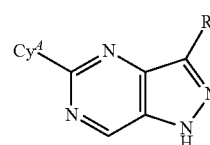
[0006] The present disclosure further provides methods of inhibiting HPK1 activity, which comprises administering to an individual a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

[0007] The present disclosure further provides methods of treating a disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

## DETAILED DESCRIPTION

### Compounds

[0008] The present disclosure provides, a compound of Formula (I):



[0009] or a pharmaceutically acceptable salt thereof, wherein:

[0010] R¹ is selected from Cy¹, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, 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>)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 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 R<sup>10</sup>;

[0011] Cy¹ is selected from C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 mem-

bered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

**[0012]** Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of the 5-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R<sup>20</sup>;

**[0013]** each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, NO<sub>2</sub>, OR<sup>a1</sup>, SR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, OC(O)R<sup>b1</sup>, OC(O)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(O)R<sup>b1</sup>, NR<sup>c1</sup>C(O)OR<sup>a1</sup>, NR<sup>c1</sup>C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(=NR<sup>e1</sup>)R<sup>b1</sup>, C(=NOR<sup>a1</sup>)R<sup>b1</sup>, C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>S(O)R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>, S(O)R<sup>b1</sup>, S(O)NR<sup>c1</sup>R<sup>d1</sup>, S(O)<sub>2</sub>R<sup>b1</sup>, and S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

**[0014]** or two R<sup>10</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3, ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

**[0015]** each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a3</sup>, SR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>c3</sup>R<sup>d3</sup>, NR<sup>c3</sup>C(O)R<sup>b3</sup>, NR<sup>c3</sup>C(O)OR<sup>a3</sup>, NR<sup>c3</sup>C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(=NR<sup>e3</sup>)R<sup>b3</sup>, C(=NOR<sup>a3</sup>)R<sup>b3</sup>, C(=NR<sup>e3</sup>)NR<sup>c3</sup>R<sup>d3</sup>, NR<sup>c3</sup>C(=NR<sup>e3</sup>)NR<sup>c3</sup>R<sup>d3</sup>, NR<sup>c3</sup>S(O)R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>, S(O)R<sup>b3</sup>, S(O)NR<sup>c3</sup>R<sup>d3</sup>, S(O)<sub>2</sub>R<sup>b3</sup>, and S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

**[0016]** each R<sup>12</sup> is independently selected from 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>3-6</sub> cycloalkyl,

C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a5</sup>, SR<sup>a5</sup>, C(O)R<sup>b5</sup>, C(O)NR<sup>c5</sup>R<sup>d5</sup>, C(O)OR<sup>a5</sup>, NR<sup>c5</sup>R<sup>d5</sup>, NR<sup>c5</sup>C(O)R<sup>b5</sup>, NR<sup>c5</sup>C(O)OR<sup>a5</sup>, NR<sup>c5</sup>S(O)R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>, S(O)R<sup>b5</sup>, S(O)NR<sup>c5</sup>R<sup>d5</sup>, S(O)<sub>2</sub>R<sup>b5</sup>, and S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>5</sup>;

**[0017]** each R<sup>20</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, 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>, 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>, C(=NR<sup>e2</sup>)R<sup>b2</sup>, C(=NOR<sup>a2</sup>)R<sup>b2</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>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>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

**[0018]** or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-7</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

**[0019]** each R<sup>21</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a4</sup>, SR<sup>a4</sup>, C(O)R<sup>b4</sup>, C(O)NR<sup>c4</sup>R<sup>d4</sup>, C(O)OR<sup>a4</sup>, NR<sup>c4</sup>R<sup>d4</sup>, NR<sup>c4</sup>C(O)R<sup>b4</sup>, NR<sup>c4</sup>C(O)OR<sup>a4</sup>, NR<sup>c4</sup>S(O)R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>, S(O)R<sup>b4</sup>, S(O)NR<sup>c4</sup>R<sup>d4</sup>, S(O)<sub>2</sub>R<sup>b4</sup>, and S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

**[0020]** or two R<sup>21</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl

ring has at least one ring-forming carbon atom and 1, 2 or 3 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>22</sup>;

**[0021]** each R<sup>22</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a6</sup>, SR<sup>a6</sup>, C(O)R<sup>b6</sup>, C(O)NR<sup>c6</sup>R<sup>d6</sup>, C(O)OR<sup>a6</sup>, NR<sup>c6</sup>R<sup>d6</sup>, NR<sup>c6</sup>C(O)R<sup>b6</sup>, NR<sup>c6</sup>C(O)OR<sup>a6</sup>, NR<sup>c6</sup>S(O)R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>, S(O)R<sup>b6</sup>, S(O)NR<sup>c6</sup>R<sup>d6</sup>, S(O)<sub>2</sub>R<sup>b6</sup>, and S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>g</sup>;

**[0022]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;

**[0023]** or any R<sup>c</sup> and R<sup>d</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

**[0024]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;

**[0025]** each R<sup>e</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

**[0026]** each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

**[0027]** or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

**[0028]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl,

C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

**[0029]** each R<sup>e1</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

**[0030]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

**[0031]** or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

**[0032]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

**[0033]** each R<sup>e2</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

**[0034]** each R<sup>a3</sup>, R<sup>b3</sup> and R<sup>d3</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

**[0035]** or any R<sup>c3</sup> and R<sup>d3</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>12</sup>;

**[0036]** each R<sup>b3</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

**[0037]** each R<sup>a4</sup>, R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;



[0038] or any  $R^{c4}$  and  $R^{d4}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from  $R^{22}$ ;

[0039] each  $R^{b4}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said  $C_{1-6}$  alkyl  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{22}$ ;

[0040] each  $R^{a5}$ ,  $R^{c5}$  and  $R^{d5}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ;

[0041] each  $R^{b5}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ;

[0042] each  $R^{a6}$ ,  $R^{c6}$  and  $R^{d6}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ;

[0043] each  $R^{b6}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ; and

[0044] each  $R^8$  is independently selected from OH,  $NO_2$ , CN, halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-2}$  alkylene,  $C_{1-6}$  alkoxy,  $C_{1-6}$  haloalkoxy,  $C_{1-3}$  alkoxy- $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy- $C_{1-3}$  alkoxy,  $HO-C_{1-3}$  alkoxy,  $HO-C_{1-3}$  alkyl, cyano- $C_{1-3}$  alkyl,  $H_2N-C_{1-3}$  alkyl, 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, 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;

[0045] provided that:

[0046] 1)  $R^1$  is other than  $NH_2$ ;

[0047] 2)  $R^1$  is other than  $CH_3$ ;

[0048] 3)  $R^1$  is other than  $CH_2$ (quinolin-6-yl);

[0049] 4)  $R^1$  is other than  $NHC(O)CH_2CH_2CH_3$ ; and

[0050] 5) when  $Cy^1$  is unsubstituted or substituted pyrazol-4-yl, then  $R^1$  is other than pyridin-4-yl substituted by morpholine.

[0051] In some embodiments,  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cS(O)R^b$ ,  $NR^cS(O)_2R^b$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ .

[0052] In certain embodiments,  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ , and  $NR^cC(O)R^b$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ . In some embodiments,  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $OR^a$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ . For example,  $R^1$  can be selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ . In certain embodiments,  $R^1$  is  $Cy^1$  or  $C_{2-6}$  alkenyl; wherein said  $C_{2-6}$  alkenyl is optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{10}$ . In certain embodiments,  $R^1$  is selected from  $Cy^1$ ,  $C(O)NR^cR^d$  and  $NR^cC(O)R^b$ . In certain embodiments,  $R^1$  is selected from phenyl, pyridinyl, pyrazolyl, thiazolyl,  $C(O)NR^cR^d$  and  $NR^cC(O)R^b$ ; wherein the phenyl, pyridinyl, pyrazolyl, and thiazolyl are each optionally substituted with 1, 2 or 3 substituents independently selected from  $R^{10}$ .

[0053] In some embodiments,  $R^1$  is not  $C_{1-6}$  alkyl that is optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$  (e.g.,  $CH_3$  and  $CH_2$ (quinolin-6-yl)). In certain embodiments,  $R^1$  is not  $NR^cR^d$  (e.g.,  $NH_2$ ). In some embodiments,  $R^1$  is  $NR^cC(O)R^b$  but not including  $NHC(O)CH_2CH_2CH_3$ .

[0054] In some embodiments,  $R^1$  is  $C_{2-6}$  alkenyl; wherein said  $C_{2-6}$  alkenyl is optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{10}$ . For example,  $R^1$  can be  $CHCH$  substituted with  $R^{10}$ , and  $R^{10}$  is phenyl substituted with 4-methylpiperazin-1-yl.

[0055] In some embodiments,  $R^1$  is  $Cy^1$ .

[0056] In some embodiments,  $Cy^1$  is selected from 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ .

[0057] In some embodiments,  $Cy^1$  is  $C_{6-10}$  aryl or 5-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ .

[0058] In some embodiments,  $Cy^1$  is  $C_{6-10}$  aryl optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ . In certain embodiments,  $Cy^1$  is 5-10 membered heteroaryl optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ . For example,  $Cy^1$  can be phenyl, pyrazolyl, pyridinyl, pyrimidinyl, thiophenyl, and pyridone; wherein the phenyl, pyrazolyl, pyridi-



**[0070]** In some embodiments, each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl, 4-10 membered heterocycloalkyl, CN,  $OR^{a3}$ ,  $C(O)R^{b3}$ ,  $NR^{c3}R^{d3}$ ,  $NR^{c3}S(O)_2R^{b3}$ , and  $S(O)_2R^{b3}$ ; wherein said  $C_{1-6}$  alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ .

**[0071]** In some embodiments, each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl, 4-10 membered heterocycloalkyl, CN,  $C(O)R^{b3}$ , and  $NR^{c3}R^{d3}$ ; wherein said  $C_{1-6}$  alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ .

**[0072]** In some embodiments, each  $R^{11}$  is independently selected from  $C_{1-3}$  alkyl, 4-10 membered heterocycloalkyl, CN,  $C(O)R^{b3}$ , and  $NR^{c3}R^{d3}$ ; wherein said  $C_{1-3}$  alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ . In some embodiments, each  $R^{11}$  is  $C_{1-3}$  alkyl optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ .

**[0073]** In some embodiments, each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^{a5}$ ,  $SR^{a5}$ ,  $C(O)R^{b5}$ ,  $C(O)NR^{c5}R^{d5}$ ,  $C(O)OR^{a5}$ ,  $NR^{c5}R^{d5}$ , or  $NR^{c5}C(O)R^{b5}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ .

**[0074]** In some embodiments, each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, and  $OR^{a5}$ . For example, each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, and halo. In some embodiments, each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl. For example, each  $R^{12}$  is  $C_{1-6}$  alkyl. In some embodiments, each  $R^{12}$  is independently  $OR^{a5}$ . In some embodiments, each  $R^{12}$  is independently  $C_{1-6}$  alkyl.

**[0075]** In some embodiments,  $R^{10}$  is 4-methylpiperazin-1-yl, fluoro, methyl, CN, trifluoromethyl, methoxy, N,N-dimethylaminocarbonyl, (4-methylpiperazin-1-yl)methyl, 4-morpholinylmethyl, morpholinyl, piperazin-1-yl, pyrrolidin-1-yl, N,N-dimethylamine, morpholinylmethanone, N-cyclopentylaminocarbonyl, 4-(cycloprop-1-yl)morpholinyl, cyanomethyl, 4-ethylpiperazin-1-yl, N-methylaminocarbonyl, cyclopropyl, pyridin-1-yl, methylamine, 1-methyl-1-cyanomethyl, tetrahydro-2H-pyran-4-yl, phenyl, 1-(piperazin-1-yl)ethan-1-one, 3-hydroxy-piperidin-1-yl, 4-cyano-piperidin-1-yl, 3-hydroxy-pyrrolidin-1-yl, piperidin-4-yl, 4-(2-methyl-2-hydroxypropyl)piperazin-1-yl, 3-methyl-3-(methylhydroxy)piperidin-1-yl, 1-(methylsulfonyl)piperidin-4-amino, 4-(ethylhydroxy)piperazin-1-yl, 4-(methylsulfonyl)piperazin-1-yl, 4-((N-methyl-N-ethyl)aminocarbonyl)piperazin-1-yl, piperidin-1-yl, 4-(methylcarbamoyl)piperazin-1-yl, 2-cyanophenyl, 1-hydroxyethane-2-amino, (methylsulfonyl)amino-methyl, azetidin-1-ylsulfonyl, difluoromethoxy, 2-(methoxymethyl)morpholin-4-yl, 4-methyl-4-hydroxypiperidin-1-yl, or 4-(2-methoxyethyl)piperazin-1-yl.

**[0076]** Examples of  $R^{10}$  can include 4-methylpiperazin-1-yl, fluoro, methyl, CN, trifluoromethyl, methoxy, N,N-dimethylaminocarbonyl, (4-methylpiperazin-1-yl)methyl, 4-morpholinylmethyl, morpholinyl, piperazin-1-yl, pyrrolidin-1-yl, N,N-dimethylamine, morpholinylmethanone, N-cyclopentylaminocarbonyl, 4-(cycloprop-1-yl)morpholine, cyanomethyl, 4-ethylpiperazin-1-yl, N-methylamin-

ocarbonyl, cyclopropyl, pyridin-1-yl, methylamine, 1-methyl-1-cyanomethyl, tetrahydro-2H-pyran-4-yl, phenyl, and 1-(piperazin-1-yl)ethan-1-one.

**[0077]** In some embodiments,  $R^{10}$  is 4-ethylpiperazin-1-yl.

**[0078]** In some embodiments,  $Cy^4$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 6-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{20}$ .

**[0079]** In some embodiments,  $Cy^4$  is  $C_{6-10}$  aryl. In some embodiments,  $Cy^4$  is 6-10 membered heteroaryl. In certain embodiments,  $Cy^4$  is not 5-membered heteroaryl (e.g., unsubstituted or substituted pyrazol-4-yl).

**[0080]** In some embodiments,  $Cy^4$  is phenyl, pyridinyl, isoindolin-1-onyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolinyl, 2,3-dihydro-1H-inden-5-yl, or 1,2,3,4-tetrahydronaphthyl; wherein the phenyl, pyridinyl, isoindolin-1-onyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolinyl, 2,3-dihydro-1H-inden-5-yl, and 1,2,3,4-tetrahydronaphthyl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{20}$ .

**[0081]** In some embodiments,  $Cy^4$  is phenyl, pyridinyl, isoindolin-1-onyl, or 1,2,3,4-tetrahydroisoquinolinyl; wherein the phenyl, pyridinyl, isoindolin-1-onyl, and 1,2,3,4-tetrahydroisoquinolinyl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{20}$ .

**[0082]** In some embodiments,  $Cy^4$  is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{20}$ .

**[0083]** In some embodiments,  $Cy^4$  is phenyl; or two adjacent  $R^{20}$  substituents on the  $Cy^4$  ring, taken together with the atoms to which they are attached, form a fused 5- or 6-membered heterocycloalkyl ring, or a fused  $C_{3-6}$  cycloalkyl ring; wherein the fused 5- or 6-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2 or 3 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 5- or 6-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 5- or 6-membered heterocycloalkyl ring and fused  $C_{3-6}$  cycloalkyl ring are each optionally substituted with 1, 2 or 3 substituents independently selected from  $R^{21}$ .

**[0084]** In some embodiments, each  $R^{20}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, 4-10 membered heterocycloalkyl, halo, CN,  $OR^{a2}$ ,  $SR^{a2}$ ,  $C(O)R^{b2}$ ,  $C(O)NR^{c2}R^{d2}$ ,  $C(O)OR^{a2}$ ,  $OC(O)R^{b2}$ ,  $OC(O)NR^{c2}R^{d2}$ ,  $NR^{c2}R^{d2}$ ,  $NR^{c2}C(O)R^{b2}$ ,  $NR^{c2}C(O)OR^{a2}$ ,  $NR^{c2}S(O)_2R^{b2}$ ,  $NR^{c2}S(O)_2R^{b2}$ ,  $S(O)R^{b2}$ ,  $S(O)NR^{c2}R^{d2}$ ,  $S(O)_2R^{b2}$ , and  $S(O)_2NR^{c2}R^{d2}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{21}$ ; or two adjacent  $R^{20}$  substituents on the  $Cy^4$  ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused  $C_{3-7}$  cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4

ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>.

**[0085]** In some embodiments, each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>, 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>S(O)R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>R<sup>b2</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>; 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 R<sup>21</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>.

**[0086]** In some embodiments, each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, 4-10 membered heterocycloalkyl, halo, 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>, NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; 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 R<sup>21</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1 or 2 substituents independently selected from R<sup>21</sup>.

**[0087]** In certain embodiments, each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, 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>, NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; 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 R<sup>21</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring.

**[0088]** In some embodiments, each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, 4-10 membered heterocycloalkyl, halo, OR<sup>a2</sup>, C(O)R<sup>b2</sup>, C(O)NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1 or 2 substituents independently selected from R<sup>21</sup>.

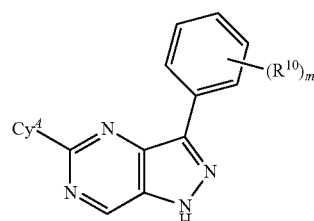
**[0089]** In certain embodiments, each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, halo, OR<sup>a2</sup>, C(O)R<sup>b2</sup>, and C(O)NR<sup>c2</sup>R<sup>d2</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring.

**[0090]** In some embodiments, R<sup>20</sup> is fluoro, methyl, methoxy, chloro, (morpholino)methanone, N-methylaminocarbonyl, aminocarbonyl, (methylamino)methyl, trifluoromethyl, pyrrolidin-2-yl, piperidin-2-yl, ((pyrrolidin-1-yl)methyl)carbonylamino, ((N,N-dimethylamino)methyl)carbonylamino, C(O)H, 1-(methylamino)-ethyl, (ethylamino)methyl, cyanomethyl, N-methylamino, or amino; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused piperidiny ring. For example, R<sup>20</sup> is fluoro, methyl, methoxy, chloro, (morpholino)methanone, N-methylaminocarbonyl, or aminocarbonyl; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused piperidiny ring.

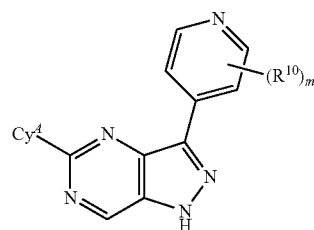
**[0091]** In some embodiments, each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, or halo; wherein said C<sub>1-6</sub> alkyl is optionally substituted with 1 or 2 substituents independently selected from R<sup>21</sup>. In some embodiments, R<sup>20</sup> is halo (e.g., fluoro). In some embodiments, R<sup>20</sup> is C<sub>1-6</sub> haloalkyl (e.g., trifluoromethyl). In some embodiments, C<sub>1-6</sub> alkyl is optionally substituted with 1 substituent independently selected from R<sup>21</sup> (e.g., R<sup>20</sup> is (methylamino)methyl). In some embodiments, R<sup>20</sup> is fluoro, trifluoromethyl or (methylamino)methyl.

**[0092]** In some embodiments, Cy<sup>4</sup> is 2-fluoro-6-methoxyphenyl. In some embodiments, Cy<sup>4</sup> is phenyl substituted with halo (e.g., fluoro), C<sub>1-6</sub> haloalkyl (e.g., trifluoromethyl), and C<sub>1-6</sub> alkyl substituted with 1 substituent independently selected from R<sup>21</sup> (e.g., R<sup>20</sup> is (methylamino)methyl). In some embodiments, Cy<sup>4</sup> is phenyl substituted with fluoro, trifluoromethyl, and (methylamino)methyl.

**[0093]** In some embodiments, provided herein is a compound having Formula (IIa1), Formula (IIa2), Formula (IIa3), Formula (IIa4) or Formula (IIa5):

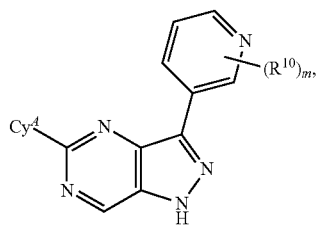


IIa1



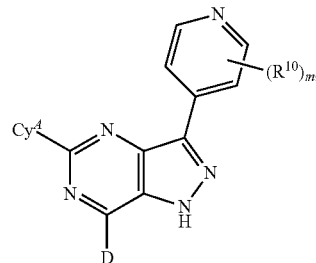
IIa2

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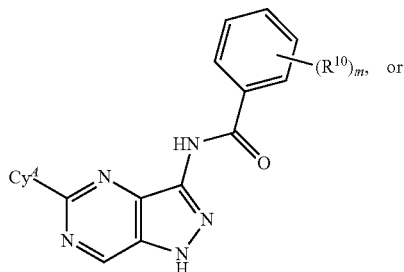
IIa3

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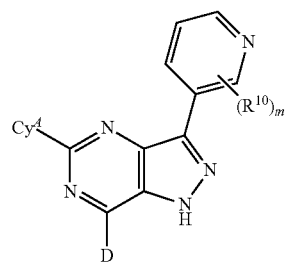


IIa2'

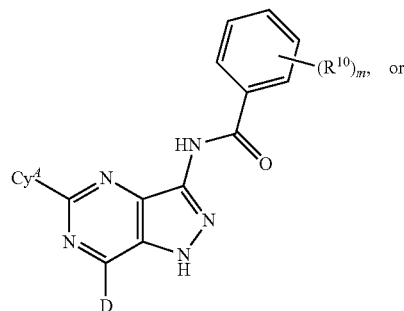
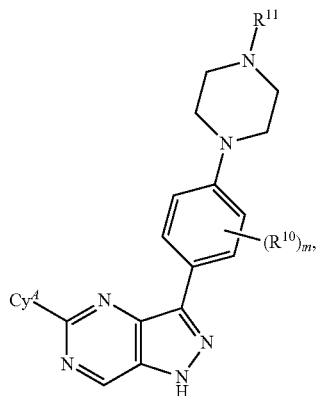
IIa4



IIa5



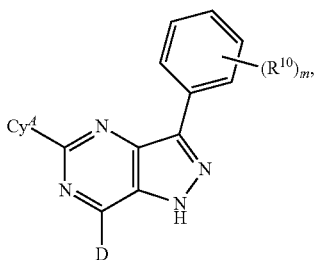
IIa3'



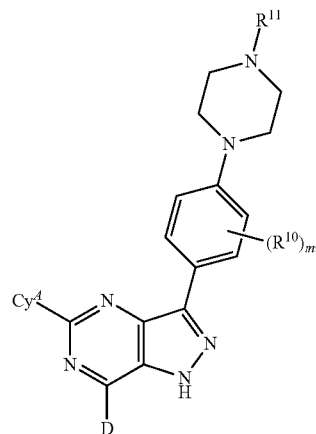
IIa4'

or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0, 1, 2, 3, or 4; and variables  $Cy^A$ ,  $R^{10}$ , and  $R^{11}$  are as defined herein.

**[0094]** In some embodiments, one or more hydrogen atoms in a compound of the present disclosure can be replaced or substituted by deuterium. For example, the compound can be a compound of Formula (IIa1'), Formula (IIa2'), Formula (IIa3'), Formula (IIa4') or Formula (IIa5'):



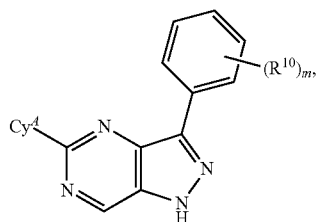
IIa1'



IIa5'

or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0, 1, 2, 3, or 4;  $R^{10}$ ,  $R^{11}$  and  $Cy^A$  are as defined herein, and wherein one or more hydrogen atoms of  $R^{10}$ ,  $R^{11}$ , and  $Cy^A$  are optionally substituted or replaced with one or more deuterium.

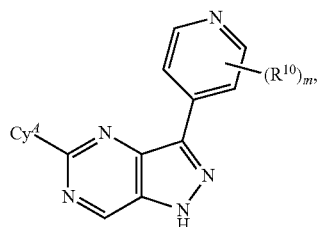
**[0095]** In some embodiments, provided herein is a compound having Formula (IIa1):



IIa1

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; and variables Cy<sup>A</sup> and R<sup>10</sup> are as defined herein.

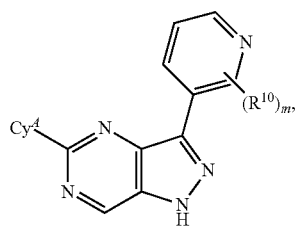
**[0096]** In some embodiments, provided herein is a compound having Formula (IIa2):



(IIa2)

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; and variables Cy<sup>A</sup> and R<sup>10</sup> are as defined herein.

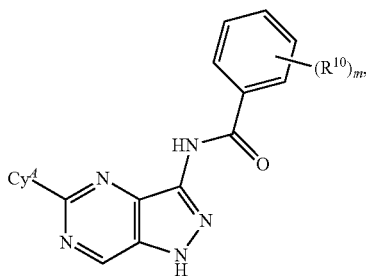
**[0097]** In some embodiments, provided herein is a compound having Formula (IIa3):



(IIa3)

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; and variables Cy<sup>A</sup> and R<sup>10</sup> are as defined herein.

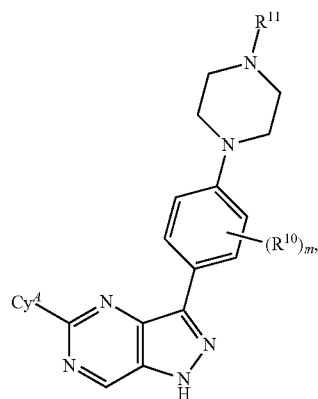
**[0098]** In some embodiments, provided herein is a compound having Formula (IIa4):



(IIa4)

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; and variables Cy<sup>A</sup> and R<sup>10</sup> are as defined herein.

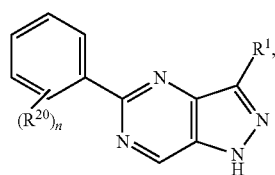
**[0099]** In some embodiments, provided herein is a compound having Formula (IIa5):



(IIa5)

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; and variables Cy<sup>A</sup>, R<sup>10</sup>, and R<sup>11</sup> are as defined herein.

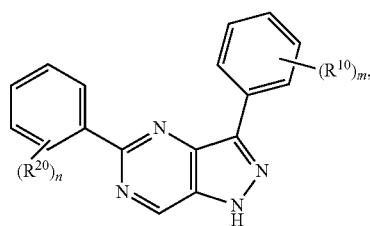
**[0100]** In some embodiments, provided herein is a compound having Formula (IIb1):



IIb1

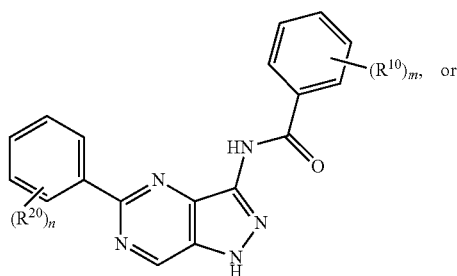
or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, 2, 3, 4 or 5; and variables R<sup>20</sup> and R<sup>1</sup> are as defined herein.

**[0101]** In some embodiments, provided herein is a compound having Formula (IIc1), Formula (IIc2) or Formula (IIc3):



IIc1

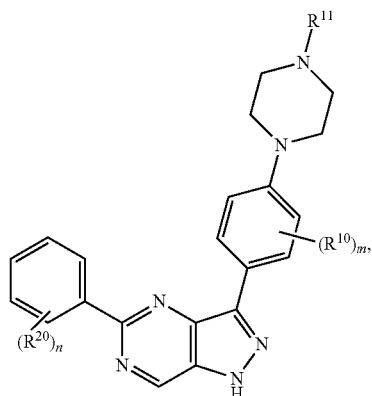
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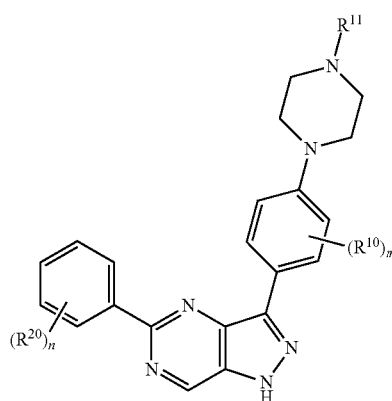
IIc2

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; n is 0, 1, 2, 3, 4, or 5; and variables  $R^{10}$  and  $R^{20}$  are as defined herein.

**[0104]** In some embodiments, the compound provided herein is a compound Formula (IIc3):



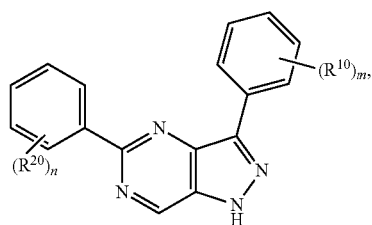
IIc3



IIc3

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; n is 0, 1, 2, 3, 4, or 5; and variables  $R^{10}$ ,  $R^{11}$ , and  $R^{20}$  are as defined herein.

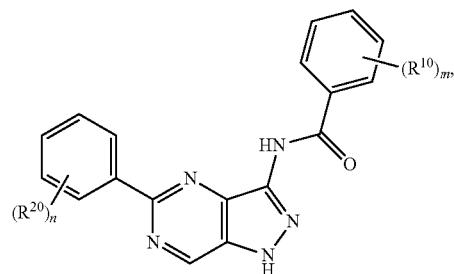
**[0102]** In some embodiments, the compound provided herein is a compound Formula (IIc1):



IIc1

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; n is 0, 1, 2, 3, 4, or 5; and variables  $R^{10}$  and  $R^{20}$  are as defined herein.

**[0103]** In some embodiments, the compound provided herein is a compound Formula (IIc2):



IIc2

or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; n is 0, 1, 2, 3, 4, or 5; and variables  $R^{10}$ ,  $R^{11}$ , and  $R^{20}$  are as defined herein.

**[0105]** In some embodiments, m is 0.

**[0106]** In some embodiments, m is 1.

**[0107]** In some embodiments, m is 2.

**[0108]** In some embodiments, n is 1.

**[0109]** In some embodiments, n is 2.

**[0110]** In some embodiments, n is 3.

**[0111]** The disclosure also provided herein a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

**[0112]**  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $NO_2$ ,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cC(O)NR^cR^d$ ,  $C(=NR^e)R^b$ ,  $C(=NOR^a)R^b$ ,  $C(=NR^e)NR^cR^d$ ,  $NR^cC(=NR^e)NR^cR^d$ ,  $NR^cS(O)R^b$ ,  $NR^cS(O)_2R^b$ ,  $NR^cC(O)_2NR^cR^d$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

**[0113]**  $Cy^1$  is selected from  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ ;

**[0114]**  $Cy^4$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 6-10 membered heteroaryl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of the 6-10 membered

heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R<sup>20</sup>;

[0115] each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, NO<sub>2</sub>, OR<sup>a1</sup>, SR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, OC(O)R<sup>b1</sup>, OC(O)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(O)R<sup>b1</sup>, NR<sup>c1</sup>C(O)OR<sup>a1</sup>, NR<sup>c1</sup>C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(=NR<sup>e1</sup>)R<sup>b1</sup>, C(=NOR<sup>a1</sup>)R<sup>b1</sup>, C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>S(O)R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>, S(O)R<sup>b1</sup>, S(O)NR<sup>c1</sup>R<sup>d1</sup>, S(O)<sub>2</sub>R<sup>b1</sup>, and S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

[0116] or two R<sup>10</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3, ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

[0117] each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a3</sup>, SR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>c3</sup>R<sup>d3</sup>, NR<sup>c3</sup>C(O)R<sup>b3</sup>, NR<sup>c3</sup>C(O)OR<sup>a3</sup>, NR<sup>c3</sup>S(O)R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>, S(O)R<sup>b3</sup>, S(O)NR<sup>c3</sup>R<sup>d3</sup>, S(O)<sub>2</sub>R<sup>b3</sup>, and S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

[0118] each R<sup>12</sup> is independently selected from 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>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a5</sup>, SR<sup>a5</sup>, C(O)R<sup>b5</sup>, C(O)NR<sup>c5</sup>R<sup>d5</sup>, C(O)OR<sup>a5</sup>, NR<sup>c5</sup>R<sup>d5</sup>, NR<sup>c5</sup>C(O)R<sup>b5</sup>, NR<sup>c5</sup>C(O)OR<sup>a5</sup>, NR<sup>c5</sup>S(O)R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>, S(O)R<sup>b5</sup>, S(O)NR<sup>c5</sup>R<sup>d5</sup>, S(O)<sub>2</sub>R<sup>b5</sup>, and S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>8</sup>;

[0119] each R<sup>20</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, NO<sub>2</sub>, OR<sup>a2</sup>, SR<sup>a2</sup>, C(O)OR<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>, 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>, C(=NR<sup>e2</sup>)R<sup>b2</sup>, C(=NOR<sup>a2</sup>)R<sup>b2</sup>, (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>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>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

[0120] or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0121] each R<sup>21</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a4</sup>, SR<sup>a4</sup>, S(O)R<sup>b4</sup>, C(O)NR<sup>c4</sup>R<sup>d4</sup>, C(O)OR<sup>a4</sup>, NR<sup>c4</sup>R<sup>d4</sup>, NR<sup>c4</sup>C(O)R<sup>b4</sup>, NR<sup>c4</sup>C(O)OR<sup>a4</sup>, NR<sup>c4</sup>S(O)R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>, S(O)R<sup>b4</sup>, S(O)NR<sup>c4</sup>R<sup>d4</sup>, S(O)<sub>2</sub>R<sup>b4</sup>, and S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

[0122] or two R<sup>21</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>22</sup>;

[0123] each R<sup>22</sup> is independently selected from 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>3-6</sub> cycloalkyl,



phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a6</sup>, SR<sup>a6</sup>, C(O)R<sup>b6</sup>, C(O)NR<sup>c6</sup>R<sup>d6</sup>, C(O)OR<sup>a6</sup>, NR<sup>c6</sup>R<sup>d6</sup>, NR<sup>c6</sup>C(O)R<sup>b6</sup>, NR<sup>c6</sup>C(O)OR<sup>a6</sup>, NR<sup>c6</sup>S(O)R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>, S(O)R<sup>b6</sup>, S(O)NR<sup>c6</sup>R<sup>d6</sup>, S(O)<sub>2</sub>R<sup>b6</sup>, and S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>g</sup>;

**[0124]** each R<sup>a</sup>, R<sup>c</sup>, and R<sup>d</sup> is independently selected from H, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;

**[0125]** or any R<sup>c</sup> and R<sup>d</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

**[0126]** each R<sup>b</sup> is independently selected from C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl; wherein said C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;

**[0127]** each R<sup>e</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

**[0128]** each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

**[0129]** or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

**[0130]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

**[0131]** each R<sup>e1</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

**[0132]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein

said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

**[0133]** or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

**[0134]** 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

**[0135]** each R<sup>e2</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

**[0136]** each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

**[0137]** or any R<sup>c3</sup> and R<sup>d3</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>12</sup>;

**[0138]** each R<sup>b3</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

**[0139]** each R<sup>a4</sup>, R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

**[0140]** or any R<sup>c4</sup> and R<sup>d4</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>22</sup>;

**[0141]** each R<sup>b4</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

[0142] each  $R^{a5}$ ,  $R^{c5}$  and  $R^{d5}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^g$ ;

[0143] each  $R^{b5}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^g$ ;

[0144] each  $R^{a6}$ ,  $R^{c6}$  and  $R^{d6}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^g$ ;

[0145] each  $R^{b6}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^g$ ; and

[0146] each  $R^g$  is independently selected from OH,  $NO_2$ , CN, halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-2}$  alkylene,  $C_{1-6}$  alkoxy,  $C_{1-6}$  haloalkoxy,  $C_{1-3}$  alkoxy- $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy- $C_{1-3}$  alkoxy,  $HO-C_{1-3}$  alkoxy,  $HO-C_{1-3}$  alkyl, cyano- $C_{1-3}$  alkyl,  $H_2N-C_{1-3}$  alkyl, 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, 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.

[0147] In some embodiments:

[0148]  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cS(O)R^b$ ,  $NR^cS(O)_2R^b$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

[0149]  $Cy^1$  is selected from 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ ;

[0150]  $Cy^A$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from  $R^{20}$ ;

[0151] each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $NO_2$ ,  $OR^{a1}$ ,  $SR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $OC(O)R^{b1}$ ,  $OC(O)NR^{c1}R^{d1}$ ,  $NR^{c1}R^{d1}$ ,  $NR^{c1}C(O)R^{b1}$ ,  $NR^{c1}C(O)OR^{a1}$ ,  $NR^{c1}S(O)R^{b1}$ ,  $NR^{c1}S(O)_2R^{b1}$ ,  $S(O)R^{b1}$ ,  $S(O)NR^{c1}R^{d1}$ ,  $S(O)_2R^{b1}$ , and  $S(O)_2NR^{c1}R^{d1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ ;

[0152] each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl, halo, CN,  $OR^{a3}$ ,  $SR^{a3}$ ,  $C(O)R^{b3}$ ,  $C(O)NR^{c3}R^{d3}$ ,  $C(O)OR^{a3}$ ,  $NR^{c3}R^{d3}$ ,  $NR^{c3}C(O)R^{b3}$ , and  $NR^{c3}C(O)OR^{a3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ ;

[0153] each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo,  $OR^{a5}$ ,  $SR^{a5}$ ,  $C(O)R^{b5}$ ,  $C(O)NR^{c5}R^{d5}$ ,  $C(O)OR^{a5}$ ,  $NR^{c5}R^{d5}$ ,  $NR^{c5}C(O)R^{b5}$ , and  $NR^{c5}C(O)OR^{a5}$ ;

[0154] each  $R^{20}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^{a2}$ ,  $SR^{a2}$ ,  $C(O)R^{b2}$ ,  $C(O)NR^{c2}R^{d2}$ ,  $C(O)OR^{a2}$ ,  $OC(O)R^{b2}$ ,  $OC(O)NR^{c2}R^{d2}$ ,  $NR^{c2}R^{d2}$ ,  $NR^{c2}C(O)R^{b2}$ ,  $NR^{c2}C(O)OR^{a2}$ ,  $NR^{c2}S(O)R^{b2}$ ,  $NR^{c2}S(O)_2R^{b2}$ ,  $S(O)R^{b2}$ ,  $S(O)NR^{c2}R^{d2}$ ,  $S(O)_2R^{b2}$ , and  $S(O)_2NR^{c2}R^{d2}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{21}$ ;

[0155] or two adjacent  $R^{20}$  substituents on the  $Cy^A$  ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused  $C_{3-7}$  cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused  $C_{3-6}$  cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{21}$ ;

[0156] each  $R^{21}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo,  $OR^{a4}$ ,  $SR^{a4}$ ,  $C(O)R^{b4}$ ,  $C(O)NR^{c4}R^{d4}$ ,  $C(O)OR^{a4}$ ,  $NR^{c4}R^{d4}$ ,  $NR^{c4}C(O)R^{b4}$ , and  $NR^{c4}C(O)OR^{a4}$ ;

[0157] each  $R^a$ ,  $R^c$ , and  $R^d$  is independently selected from H,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl

are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

**[0158]** each  $R^b$  is independently selected from  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 5-10 membered heteroaryl; wherein said  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

**[0159]**  $R^{a1}$ ,  $R^{c1}$  and  $R^{d1}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ ;

**[0160]** or any  $R^{c1}$  and  $R^{d1}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{11}$ ;

**[0161]** each  $R^{b1}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl;

**[0162]** each  $R^{a2}$ ,  $R^{c2}$  and  $R^{d2}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

**[0163]** or any  $R^{c2}$  and  $R^{d2}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{11}$ ;

**[0164]** each  $R^{b2}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl;

**[0165]** each  $R^{a3}$ ,  $R^{c3}$  and  $R^{d3}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

**[0166]** each  $R^{b3}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

**[0167]** each  $R^{a4}$ ,  $R^{c4}$  and  $R^{d4}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

**[0168]** each  $R^{b4}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

**[0169]** each  $R^{a5}$ ,  $R^{c5}$  and  $R^{d5}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; and

**[0170]** each  $R^{b5}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl.

**[0171]** In some embodiments:

**[0172]**  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ , and  $NR^cC(O)R^b$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

**[0173]**  $Cy^1$  is selected from 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom

and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ ;

**[0174]**  $Cy^4$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from  $R^{20}$ ;

**[0175]** each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $NR^{c1}R^{d1}$ , and  $NR^{c1}C(O)R^{b1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ ;

**[0176]** each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl, halo, CN,  $OR^{a3}$ ,  $C(O)R^{b3}$ ,  $C(O)NR^{c3}R^{d3}$ ,  $C(O)OR^{a3}$ ,  $NR^{c3}R^{d3}$ , and  $NR^{c3}C(O)R^{b3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ ;

**[0177]** each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, and halo;

**[0178]** each  $R^{20}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^{a2}$ ,  $C(O)R^{b2}$ ,  $C(O)NR^{c2}R^{d2}$ ,  $C(O)OR^{a2}$ ,  $NR^{c2}R^{d2}$ , and  $NR^{c2}C(O)R^{b2}$ ;

**[0179]** or two adjacent  $R^{20}$  substituents on the  $Cy^4$  ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused  $C_{3-7}$  cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused  $C_{3-6}$  cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{21}$ ;

**[0180]** each  $R^{21}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, and halo;

**[0181]** each  $R^a$ ,  $R^c$ , and  $R^d$  is independently selected from H,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0182] each  $R^b$  is independently selected from  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0183] each  $R^{a1}$ ,  $R^{c1}$  and  $R^{d1}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0184] or any  $R^{c1}$  and  $R^{d1}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{11}$ ;

[0185] each  $R^{b1}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, and 4-10 membered heterocycloalkyl;

[0186] each  $R^{a2}$ ,  $R^{c2}$  and  $R^{d2}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0187] or any  $R^{c2}$  and  $R^{d2}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{21}$ ;

[0188] each  $R^{b2}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, and 4-10 membered heterocycloalkyl;

[0189] each  $R^{a3}$ ,  $R^{c3}$  and  $R^{d3}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl; and

[0190] each  $R^{b3}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl.

[0191] In some embodiments:

[0192]  $R^1$  is selected from  $Cy^1$  and  $C_{2-6}$  alkenyl; wherein said  $C_{2-6}$  alkenyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

[0193]  $Cy^1$  is selected from 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ ;

[0194]  $Cy^4$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from  $R^{20}$ ;

[0195] each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ , and  $NR^{c1}R^{d1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ ;

[0196] each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl, 4-10 membered heterocycloalkyl, CN,  $C(O)R^{b3}$ , and  $NR^{c3}R^{d3}$ ; wherein said  $C_{1-6}$  alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ ;

[0197] each  $R^{12}$  is independently  $C_{1-6}$  alkyl;

[0198] each  $R^{20}$  is independently selected from  $C_{1-6}$  alkyl, halo,  $OR^{a2}$ ,  $C(O)R^{b2}$ , and  $C(O)NR^{c2}R^{d2}$ ;

[0199] or two adjacent  $R^{20}$  substituents on the  $Cy^4$  ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group;

[0200] each  $R^{a1}$ ,  $R^{c1}$  and  $R^{d1}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0201] or any  $R^{c1}$  and  $R^{d1}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{11}$ ;

[0202] each  $R^{b1}$  is independently  $C_{3-10}$  cycloalkyl or 4-10 membered heterocycloalkyl;

[0203] each  $R^{a2}$ ,  $R^{c2}$  and  $R^{d2}$  is independently selected from H and  $C_{1-6}$  alkyl;

[0204] or any  $R^{c2}$  and  $R^{d2}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

[0205] each  $R^{b2}$  is independently 4-10 membered heterocycloalkyl;

[0206] each  $R^{c3}$  and  $R^{d3}$  is H; and

[0207] each  $R^{b3}$  is  $C_{1-6}$  alkyl.

[0208] In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

[0209]  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo,  $NO_2$ ,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^{c1}R^{d1}$ ,  $NR^{c1}C(O)R^b$ ,  $NR^{c1}C(O)OR^a$ ,  $NR^{c1}C(O)NR^{c2}R^{d2}$ ,  $C(=NR^e)R^b$ ,  $C(=NOR^e)R^b$ ,  $C(=NR^e)NR^{c1}R^{d1}$ ,  $NR^{c1}C(=NR^e)NR^{c2}R^{d2}$ ,  $NR^{c1}S(O)R^b$ ,  $NR^{c1}S(O)_2R^b$ ,  $NR^{c1}S(O)_2NR^{c2}R^{d2}$ ,  $S(O)R^b$ ,  $S(O)NR^{c1}R^{d1}$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^{c1}R^{d1}$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

[0210]  $Cy^1$  is selected from  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ ;

[0211]  $Cy^4$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 6-10 membered heteroaryl has at least one ring-forming carbon atom and 1, 2, 3, or 4

ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R<sup>20</sup>;

[0212] each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, NO<sub>2</sub>, OR<sup>a1</sup>, SR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, OC(O)R<sup>b1</sup>, OC(O)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>e1</sup>R<sup>b1</sup>, NR<sup>c1</sup>C(O)R<sup>b1</sup>, NR<sup>c1</sup>C(O)OR<sup>a1</sup>, NR<sup>c1</sup>C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(=NR<sup>e1</sup>)R<sup>b1</sup>, C(=NOR<sup>a1</sup>)R<sup>b1</sup>, C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>S(O)R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>, S(O)R<sup>b1</sup>, S(O)NR<sup>c1</sup>R<sup>d1</sup>, S(O)<sub>2</sub>R<sup>b1</sup>, and S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

[0213] or two R<sup>10</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3, ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

[0214] each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a3</sup>, SR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>e3</sup>R<sup>b3</sup>, NR<sup>c3</sup>C(O)R<sup>b3</sup>, NR<sup>c3</sup>C(O)OR<sup>a3</sup>, NR<sup>c3</sup>S(O)R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>, S(O)R<sup>b3</sup>, S(O)NR<sup>c3</sup>R<sup>d3</sup>, S(O)<sub>2</sub>R<sup>b3</sup>, and S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

[0215] each R<sup>12</sup> is independently selected from 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>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a5</sup>, SR<sup>a5</sup>, C(O)R<sup>b5</sup>, C(O)NR<sup>c5</sup>R<sup>d5</sup>, C(O)OR<sup>a5</sup>, NR<sup>e5</sup>R<sup>b5</sup>, NR<sup>c5</sup>C(O)R<sup>b5</sup>, NR<sup>c5</sup>C(O)OR<sup>a5</sup>, NR<sup>c5</sup>S(O)R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>, S(O)R<sup>b5</sup>, S(O)NR<sup>c5</sup>R<sup>d5</sup>, S(O)<sub>2</sub>R<sup>b5</sup>, and S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl and 4-7

membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>8</sup>;

[0216] each R<sup>20</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, 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>, NR<sup>e2</sup>R<sup>b2</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>, C(=NR<sup>e2</sup>)R<sup>b2</sup>, C(=NOR<sup>a2</sup>)R<sup>b2</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>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>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

[0217] or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0218] each R<sup>21</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a4</sup>, SR<sup>a4</sup>, C(O)R<sup>b4</sup>, C(O)NR<sup>c4</sup>R<sup>d4</sup>, C(O)OR<sup>a4</sup>, NR<sup>e4</sup>R<sup>b4</sup>, NR<sup>c4</sup>C(O)R<sup>b4</sup>, NR<sup>c4</sup>C(O)OR<sup>a4</sup>, NR<sup>c4</sup>S(O)R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>, S(O)R<sup>b4</sup>, S(O)NR<sup>c4</sup>R<sup>d4</sup>, S(O)<sub>2</sub>R<sup>b4</sup>, and S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

[0219] or two R<sup>21</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub>

cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>22</sup>;

[0220] each R<sup>22</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a6</sup>, SR<sup>a6</sup>, C(O)R<sup>b6</sup>, C(O)NR<sup>c6</sup>R<sup>d6</sup>, C(O)OR<sup>a6</sup>, NR<sup>c6</sup>R<sup>d6</sup>, NR<sup>c6</sup>C(O)R<sup>b6</sup>, NR<sup>c6</sup>C(O)OR<sup>a6</sup>, NR<sup>c6</sup>S(O)R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>, S(O)R<sup>b6</sup>, S(O)NR<sup>c6</sup>R<sup>d6</sup>, S(O)<sub>2</sub>R<sup>b6</sup>, and S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>g</sup>;

[0221] 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;

[0222] or any R<sup>c</sup> and R<sup>d</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

[0223] each R<sup>b</sup> is independently selected from C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl; wherein said C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;

[0224] each R<sup>e</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

[0225] each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

[0226] or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

[0227] 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

[0228] each R<sup>e1</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub>

alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

[0229] 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

[0230] or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0231] 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

[0232] each R<sup>e2</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;

[0233] each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

[0234] or any R<sup>c3</sup> and R<sup>d3</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>12</sup>;

[0235] each R<sup>b3</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

[0236] each R<sup>a4</sup>, R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

[0237] or any R<sup>c4</sup> and R<sup>d4</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>22</sup>;

[0238] each R<sup>b4</sup> is independently selected from 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>3-6</sub> cycloalkyl,

phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

[0239] each R<sup>a5</sup>, R<sup>c5</sup> and R<sup>d5</sup> is independently selected from H, 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; 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 R<sup>g</sup>;

[0240] each R<sup>b5</sup> is independently selected from 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; 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 R<sup>g</sup>;

[0241] each R<sup>a6</sup>, R<sup>c6</sup> and R<sup>d6</sup> is independently selected from H, 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; 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 R<sup>g</sup>;

[0242] each R<sup>b6</sup> is independently selected from 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; 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 R<sup>g</sup>; and

[0243] each R<sup>g</sup> is 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>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkyl-C<sub>1-2</sub> alkylene, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkoxy, HO—C<sub>1-3</sub> alkoxy, HO—C<sub>1-3</sub> alkyl, cyano-C<sub>1-3</sub> alkyl, H<sub>2</sub>N—C<sub>1-3</sub> alkyl, 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.

[0244] In some embodiments, wherein:

[0245] R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>S(O)R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</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>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 R<sup>10</sup>;

[0246] Cy<sup>1</sup> is selected from 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

[0247] Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at

least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from R<sup>20</sup>;

[0248] each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, NO<sub>2</sub>, OR<sup>a1</sup>, SR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, OC(O)R<sup>b1</sup>, OC(O)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(O)R<sup>b1</sup>, NR<sup>c1</sup>S(O)OR<sup>a1</sup>, NR<sup>c1</sup>S(O)R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>R<sup>b1</sup>, S(O)R<sup>b1</sup>, S(O)NR<sup>c1</sup>R<sup>d1</sup>, S(O)<sub>2</sub>R<sup>b1</sup>, and S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

[0249] each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, halo, CN, OR<sup>a3</sup>, SR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>c3</sup>R<sup>d3</sup>, NR<sup>c3</sup>C(O)R<sup>b3</sup>, and NR<sup>c3</sup>C(O)OR<sup>a3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

[0250] each R<sup>12</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, OR<sup>a5</sup>, SR<sup>a5</sup>, C(O)R<sup>b5</sup>, C(O)NR<sup>c5</sup>R<sup>d5</sup>, C(O)OR<sup>a5</sup>, NR<sup>c5</sup>R<sup>d5</sup>, NR<sup>c5</sup>C(O)R<sup>b5</sup>, and NR<sup>c5</sup>C(O)OR<sup>a5</sup>;

[0251] each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>, NR<sup>c2</sup>R<sup>d2</sup>, NR<sup>c2</sup>S(O)R<sup>b2</sup>, NR<sup>c2</sup>C(O)OR<sup>a2</sup>, NR<sup>c2</sup>S(O)R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>R<sup>b2</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>; 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 R<sup>21</sup>;

[0252] or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0253] each R<sup>21</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, OR<sup>a4</sup>, SR<sup>a4</sup>, C(O)R<sup>b4</sup>, C(O)NR<sup>c4</sup>R<sup>d4</sup>, C(O)OR<sup>a4</sup>, NR<sup>c4</sup>R<sup>d4</sup>, NR<sup>c4</sup>C(O)R<sup>b4</sup>, and NR<sup>c4</sup>C(O)OR<sup>a4</sup>;

[0254] each  $R^a$ ,  $R^c$ , and  $R^d$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

[0255] each  $R^b$  is independently selected from  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 5-10 membered heteroaryl; wherein said  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

[0256] each  $R^{a1}$ ,  $R^{c1}$  and  $R^{d1}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ ;

[0257] or any  $R^{c1}$  and  $R^{d1}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{11}$ ;

[0258] each  $R^{b1}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl;

[0259] each  $R^{a2}$ ,  $R^{c2}$  and  $R^{d2}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0260] or any  $R^{c2}$  and  $R^{d2}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{21}$ ;

[0261] each  $R^{b2}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl;

[0262] each  $R^{a3}$ ,  $R^{c3}$  and  $R^{d3}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0263] each  $R^{b3}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0264] each  $R^{a4}$ ,  $R^{c4}$  and  $R^{d4}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0265] each  $R^{b4}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

[0266] each  $R^{a5}$ ,  $R^{c5}$  and  $R^{d5}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; and

[0267] each  $R^{b5}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl.

[0268] In some embodiments, wherein:

[0269]  $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ , and  $NR^cC(O)R^b$ ; wherein said  $C_{2-6}$  alkenyl and

$C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

[0270]  $Cy^1$  is selected from 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ ;

[0271]  $Cy^4$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from  $R^{20}$ ;

[0272] each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $NR^{c1}R^{d1}$ , and  $NR^{c1}C(O)R^{b1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ ;

[0273] each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl, halo, CN,  $OR^{a3}$ ,  $C(O)R^{b3}$ ,  $C(O)NR^{c3}R^{d3}$ ,  $C(O)OR^{a3}$ ,  $NR^{c3}R^{d3}$ , and  $NR^{c3}C(O)R^{b3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ ;

[0274] each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, and halo;

[0275] each  $R^{20}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^{a2}$ ,  $C(O)R^{b2}$ ,  $C(O)NR^{c2}R^{d2}$ ,  $C(O)OR^{a2}$ ,  $NR^{c2}R^{d2}$ , and  $NR^{c2}C(O)R^{b2}$ ;

[0276] or two adjacent  $R^{20}$  substituents on the  $Cy^4$  ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused  $C_{3-7}$  cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and



fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0277] each R<sup>21</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, and halo;

[0278] 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, and C<sub>1-6</sub> haloalkyl; 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 R<sup>10</sup>

[0279] each R<sup>b</sup> is independently selected from C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, and C<sub>1-6</sub> haloalkyl;

[0280] each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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;

[0281] or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

[0282] 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, and 4-10 membered heterocycloalkyl;

[0283] 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, and C<sub>1-6</sub> haloalkyl;

[0284] or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0285] 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, C<sub>1-6</sub> haloalkyl, and 4-10 membered heterocycloalkyl;

[0286] each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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; and

[0287] each R<sup>b3</sup> is independently selected from 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.

[0288] In some embodiments:

[0289] R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>, and NR<sup>c</sup>C(O)R<sup>b</sup>; wherein said 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 R<sup>10</sup>;

[0290] Cy<sup>1</sup> is selected from 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered hetero aryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

[0291] Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and

6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from R<sup>20</sup>;

[0292] each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, NR<sup>c1</sup>R<sup>d1</sup>, and NR<sup>c1</sup>C(O)R<sup>b1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

[0293] each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, halo, CN, OR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>c3</sup>R<sup>d3</sup>, and NR<sup>c3</sup>C(O)R<sup>b3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

[0294] each R<sup>12</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, and halo;

[0295] each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, OR<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>, NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; 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 R<sup>21</sup>;

[0296] or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0297] each R<sup>21</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, and NR<sup>c4</sup>R<sup>d4</sup>;

[0298] 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, and C<sub>1-6</sub> haloalkyl; 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 R<sup>10</sup>

[0299] each R<sup>b</sup> is independently selected from C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, and C<sub>1-6</sub> haloalkyl;

[0300] each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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;

[0301] or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form

a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

[0302] 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, and 4-10 membered heterocycloalkyl;

[0303] 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, and C<sub>1-6</sub> haloalkyl;

[0304] or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

[0305] 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, C<sub>1-6</sub> haloalkyl, and 4-10 membered heterocycloalkyl;

[0306] each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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;

[0307] each R<sup>b3</sup> is independently selected from 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; and

[0308] each R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H and C<sub>1-6</sub> alkyl.

[0309] In some embodiments:

[0310] R<sup>1</sup> is selected from Cy<sup>1</sup> and C<sub>2-6</sub> alkenyl; wherein said C<sub>2-6</sub> alkenyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;

[0311] Cy<sup>1</sup> is selected from 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

[0312] Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from R<sup>20</sup>;

[0313] each R<sup>10</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, and NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

[0314] each R<sup>11</sup> is independently selected from C<sub>1-6</sub> alkyl, 4-10 membered heterocycloalkyl, CN, C(O)R<sup>b3</sup>, and NR<sup>c3</sup>R<sup>d3</sup>; wherein said C<sub>1-6</sub> alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

[0315] each R<sup>12</sup> is independently C<sub>1-6</sub> alkyl;

[0316] each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, halo, OR<sup>a2</sup>, C(O)R<sup>b2</sup>, and C(O)NR<sup>c2</sup>R<sup>d2</sup>; wherein said C<sub>1-6</sub> alkyl is optionally substituted with 1, 2, or 3, substituents independently selected from R<sup>21</sup>;

[0317] or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group;

[0318] each R<sup>21</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, and NR<sup>c4</sup>R<sup>d4</sup>;

[0319] each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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;

[0320] or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

[0321] each R<sup>b1</sup> is independently C<sub>3-10</sub> cycloalkyl or 4-10 membered heterocycloalkyl;

[0322] each R<sup>a2</sup>, R<sup>c2</sup> and R<sup>d2</sup> is independently selected from H and C<sub>1-6</sub> alkyl;

[0323] or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

[0324] each R<sup>b2</sup> is independently 4-10 membered heterocycloalkyl;

[0325] each R<sup>c3</sup> and R<sup>d3</sup> is H;

[0326] each R<sup>b3</sup> is C<sub>1-6</sub> alkyl; and

[0327] each R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H and C<sub>1-6</sub> alkyl.

[0328] It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination. Thus, it is contemplated as features described as embodiments of the compounds of Formula (I) can be combined in any suitable combination.

[0329] At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C<sub>1-6</sub> alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, C<sub>3</sub> alkyl, C<sub>4</sub> alkyl, C<sub>5</sub> alkyl and C<sub>6</sub> alkyl.

[0330] The term "n-membered," where n is an integer, typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

**[0331]** At various places in the present specification, variables defining divalent linking groups may be described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example,  $\text{—NR}(\text{CR}'\text{R}')_n\text{—}$  includes both  $\text{—NR}(\text{CR}'\text{R}')_n\text{—}$  and  $\text{—(CR}'\text{R}')_n\text{NR—}$  and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “alkyl” or “aryl” then it is understood that the “alkyl” or “aryl” represents a linking alkylene group or arylene group, respectively.

**[0332]** The term “substituted” means that an atom or group of atoms formally replaces hydrogen as a “substituent” attached to another group. The term “substituted”, unless otherwise indicated, refers to any level of substitution, e.g., mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. It is to be understood that substitution at a given atom results in a chemically stable molecule. The phrase “optionally substituted” means unsubstituted or substituted. The term “substituted” means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, e.g., oxo, can replace two hydrogen atoms.

**[0333]** The term “ $\text{C}_{n-m}$ ” indicates a range which includes the endpoints, wherein  $n$  and  $m$  are integers and indicate the number of carbons. Examples include  $\text{C}_{1-4}$ ,  $\text{C}_{1-6}$  and the like.

**[0334]** The term “alkyl” employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chained or branched. The term “ $\text{C}_{n-m}$  alkyl”, refers to an alkyl group having  $n$  to  $m$  carbon atoms. An alkyl group formally corresponds to an alkane with one C—H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl and the like.

**[0335]** The term “alkenyl” employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C—H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term “ $\text{C}_{n-m}$  alkenyl” refers to an alkenyl group having  $n$  to  $m$  carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl and the like.

**[0336]** The term “alkynyl” employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with one C—H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. The term “ $\text{C}_{n-m}$

alkynyl” refers to an alkynyl group having  $n$  to  $m$  carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

**[0337]** The term “alkylene”, employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkylene group formally corresponds to an alkane with two C—H bond replaced by points of attachment of the alkylene group to the remainder of the compound. The term “ $\text{C}_{n-m}$  alkylene” refers to an alkylene group having  $n$  to  $m$  carbon atoms. Examples of alkylene groups include, but are not limited to, ethan-1,2-diyl, ethan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, propan-1,1-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl and the like.

**[0338]** The term “alkoxy”, employed alone or in combination with other terms, refers to a group of formula  $\text{—O-alkyl}$ , wherein the alkyl group is as defined above. The term “ $\text{C}_{n-m}$  alkoxy” refers to an alkoxy group, the alkyl group of which has  $n$  to  $m$  carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), *t*-butoxy and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

**[0339]** The term “amino” refers to a group of formula  $\text{—NH}_2$ .

**[0340]** The term “carbonyl”, employed alone or in combination with other terms, refers to a  $\text{—C(=O)—}$  group, which also may be written as  $\text{C(O)}$ .

**[0341]** The term “cyano” or “nitrile” refers to a group of formula  $\text{—C}\equiv\text{N}$ , which also may be written as  $\text{—CN}$ .

**[0342]** The terms “halo” or “halogen”, used alone or in combination with other terms, refers to fluoro, chloro, bromo and iodo. In some embodiments, “halo” refers to a halogen atom selected from F, Cl, or Br. In some embodiments, halo groups are F.

**[0343]** The term “haloalkyl” as used herein refers to an alkyl group in which one or more of the hydrogen atoms has been replaced by a halogen atom. The term “ $\text{C}_{n-m}$  haloalkyl” refers to a  $\text{C}_{n-m}$  alkyl group having  $n$  to  $m$  carbon atoms and from at least one up to  $\{2(n+m)+1\}$  halogen atoms, which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include  $\text{CF}_3$ ,  $\text{C}_2\text{F}_5$ ,  $\text{CHF}_2$ ,  $\text{CH}_2\text{F}$ ,  $\text{CCl}_3$ ,  $\text{CHCl}_2$ ,  $\text{C}_2\text{Cl}_5$  and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

**[0344]** The term “haloalkoxy”, employed alone or in combination with other terms, refers to a group of formula  $\text{—O-haloalkyl}$ , wherein the haloalkyl group is as defined above. The term “ $\text{C}_{n-m}$  haloalkoxy” refers to a haloalkoxy group, the haloalkyl group of which has  $n$  to  $m$  carbons. Example haloalkoxy groups include trifluoromethoxy and the like. In some embodiments, the haloalkoxy group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

**[0345]** The term “oxo” refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to carbon, or attached to a heteroatom forming a sulfoxide or sulfone group, or an N-oxide group. In some embodiments, heterocyclic groups may be optionally substituted by 1 or 2 oxo ( $\text{=O}$ ) substituents.

**[0346]** The term “sulfido” refers to a sulfur atom as a divalent substituent, forming a thiocarbonyl group ( $\text{C=S}$ ) when attached to carbon.

**[0347]** The term “aromatic” refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (i.e., having  $(4n+2)$  delocalized  $\pi$  (pi) electrons where  $n$  is an integer).

**[0348]** The term “aryl,” employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (e.g., having 2 fused rings). The term “ $C_{n-m}$  aryl” refers to an aryl group having from  $n$  to  $m$  ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, and the like. In some embodiments, aryl groups have from 6 to about 10 carbon atoms. In some embodiments aryl groups have 6 carbon atoms. In some embodiments aryl groups have 10 carbon atoms. In some embodiments, the aryl group is phenyl. In some embodiments, the aryl group is naphthyl.

**[0349]** The term “heteroaryl” or “heteroaromatic,” employed alone or in combination with other terms, refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl has 5-14 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-10 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. In other embodiments, the heteroaryl is an eight-membered, nine-membered or ten-membered fused bicyclic heteroaryl ring. Example heteroaryl groups include, but are not limited to, pyridinyl (pyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, furanyl, thiophenyl, quinolinyl, isoquinolinyl, naphthyridinyl (including 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3- and 2,6-naphthyridine), indolyl, isoindolyl, benzothio-phenyl, benzofuranyl, benzisoxazolyl, imidazo[1,2-b]thiazolyl, purinyl, and the like. In some embodiments, the heteroaryl group is pyridone (e.g., 2-pyridone).

**[0350]** A five-membered heteroaryl ring is a heteroaryl group having five ring atoms wherein one or more (e.g., 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary five-membered ring heteroaryls include thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

**[0351]** A six-membered heteroaryl ring is a heteroaryl group having six ring atoms wherein one or more (e.g., 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl, isoindolyl, and pyridazinyl.

**[0352]** The term “cycloalkyl,” employed alone or in combination with other terms, refers to a non-aromatic hydrocarbon ring system (monocyclic, bicyclic or polycyclic), including cyclized alkyl and alkenyl groups. The term “ $C_{n-m}$

cycloalkyl” refers to a cycloalkyl that has  $n$  to  $m$  ring member carbon atoms. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups and spirocycles. Cycloalkyl groups can have 3, 4, 5, 6 or 7 ring-forming carbons ( $C_{3-7}$ ). In some embodiments, the cycloalkyl group has 3 to 6 ring members, 3 to 5 ring members, or 3 to 4 ring members. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl group is a  $C_{3-6}$  monocyclic cycloalkyl group. Ring-forming carbon atoms of a cycloalkyl group can be optionally oxidized to form an oxo or sulfido group. Cycloalkyl groups also include cycloalkylidenes. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, e.g., benzo or thienyl derivatives of cyclopentane, cyclohexane and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcamyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

**[0353]** The term “heterocycloalkyl,” employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain one or more alkenylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from nitrogen, sulfur, oxygen and phosphorus, and which has 4-10 ring members, 4-7 ring members, or 4-6 ring members. Included within the term “heterocycloalkyl” are monocyclic 4-, 5-, 6- and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can include mono- or bicyclic (e.g., having two fused or bridged rings) or spirocyclic ring systems. In some embodiments, the heterocycloalkyl group is a monocyclic group having 1, 2 or 3 heteroatoms independently selected from nitrogen, sulfur and oxygen. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally oxidized to form an oxo or sulfido group or other oxidized linkage (e.g., C(O), S(O), C(S) or S(O)<sub>2</sub>, N-oxide etc.) or a nitrogen atom can be quaternized. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the heterocycloalkyl ring, e.g., benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of heterocycloalkyl groups include azetidyl, azepanyl, dihydrobenzofuranyl, dihydrofuranyl, dihydrodipyranyl, morpholino, 3-oxa-9-azaspiro[5.5]undecanyl, 1-oxa-8-azaspiro[4.5]decanyl, piperidinyl, piperazinyl, oxopiperazinyl, pyranyl, pyrrolidinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydrodipyranyl, 1,2,3,4-tetrahydroquinoli-

nyl, 1,2,3,4-tetrahydroisoquinoliny1, 1,2,3,4-tetrahydro-naphthyl, 2,3-dihydro-1H-inden-5-yl, isoindoliny1, tropanyl, and thiomorpholino.

**[0354]** At certain places, the definitions or embodiments refer to specific rings (e.g., an azetidine ring, a pyridine ring, etc.). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring may be attached at any position of the ring, whereas an azetidin-3-yl ring is attached at the 3-position.

**[0355]** The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

**[0356]** Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. One method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, e.g., optically active acids, such as the D and L forms of tartaric acid, diacetyl-tartaric 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 diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane and the like.

**[0357]** 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.

**[0358]** In some embodiments, the compounds of the invention have the (R)-configuration. In other embodiments, the compounds have the (S)-configuration. In compounds with more than one chiral centers, each of the chiral centers in the compound may be independently (R) or (S), unless otherwise indicated.

**[0359]** Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, e.g., 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and

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

**[0360]** Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 deuterium atoms. Synthetic methods for including isotopes into organic compounds are known in the art (Deuterium Labeling in Organic Chemistry by Alan F. Thomas (New York, N.Y., Appleton-Century-Crofts, 1971; The Renaissance of H/D Exchange by Jens Atzrodt, Volker Derdau, Thorsten Fey and Jochen Zimmermann, *Angew. Chem. Int. Ed.* 2007, 7744-7765). Isotopically labeled compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

**[0361]** Substitution with heavier isotopes such as deuterium, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. (A. Kerekes et. al. *J. Med. Chem.* 2011, 54, 201-210; R. Xu et. al. *J. Label Compd. Radiopharm.* 2015, 58, 308-312).

**[0362]** The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers and isotopes of the structures depicted. The term is also meant to refer to compounds of the inventions, regardless of how they are prepared, e.g., synthetically, through biological process (e.g., metabolism or enzyme conversion), or a combination thereof.

**[0363]** All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., hydrates and solvates) or can be isolated. When in the solid state, the compounds described herein and salts thereof may occur in various forms and may, e.g., take the form of solvates, including hydrates. The compounds may be in any solid state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid state form of the compound.

**[0364]** In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, e.g., a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

**[0365]** The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials,

compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

**[0366]** The expressions, “ambient temperature” and “room temperature,” as used herein, are understood in the art, and refer generally to a temperature, e.g., a reaction temperature, that is about the temperature of the room in which the reaction is carried out, e.g., a temperature from about 20° C. to about 30° C.

**[0367]** The present invention also includes pharmaceutically acceptable salts of the compounds described herein. The term “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, e.g., from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17<sup>th</sup> Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge et al., *J. Pharm. Sci.*, 1977, 66(1), 1-19 and in Stahl et al., *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (Wiley, 2002). In some embodiments, the compounds described herein include the N-oxide forms.

## Synthesis

**[0368]** Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

**[0369]** The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

**[0370]** Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of

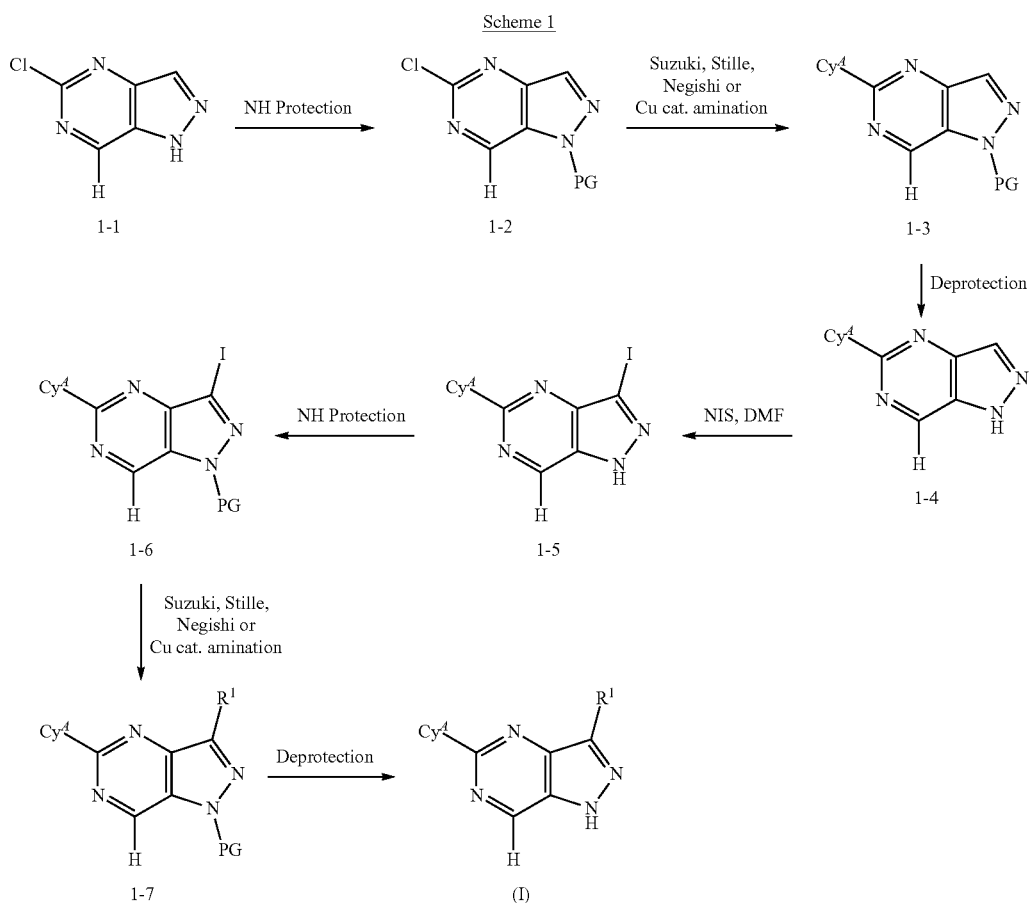
protecting groups is described, e.g., in Kocienski, *Protecting Groups*, (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith et al., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6<sup>th</sup> Ed. (Wiley, 2007); Petrusson et al., “Protecting Groups in Carbohydrate Chemistry,” *J. Chem. Educ.*, 1997, 74(11), 1297; and Wuts et al., *Protective Groups in Organic Synthesis*, 4th Ed., (Wiley, 2006).

**[0371]** Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., <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) or thin layer chromatography (TLC).

**[0372]** The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

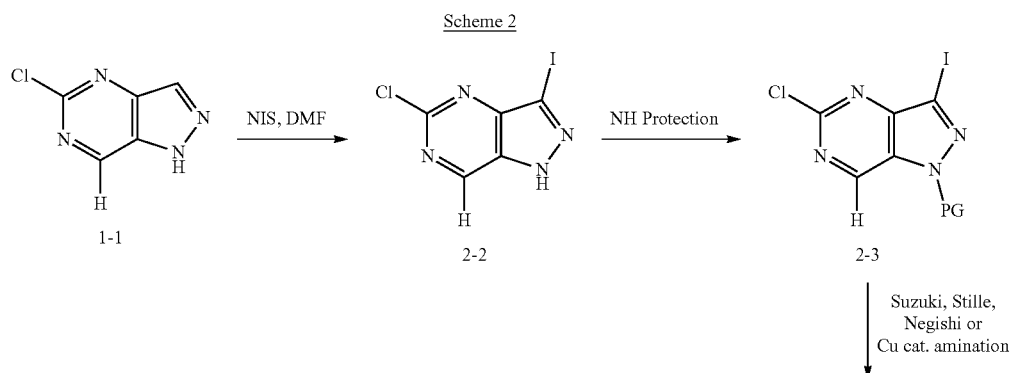
**[0373]** Compounds of Formula (I) can be prepared, e.g., using a process as illustrated in the schemes below.

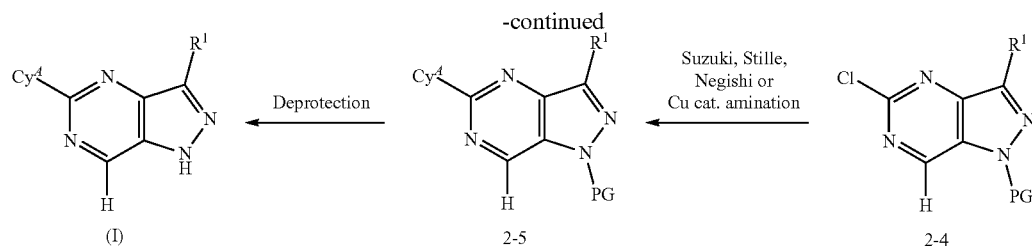
**[0374]** Compounds of Formula (I) with a variety of substitution at position R<sup>1</sup> such as those described herein can be prepared, using a process as illustrated in Scheme 1. In the process depicted in Scheme 1, compounds of Formula 1-2 is formed after protection of the NH group of the pyrazole ring of 5-chloro-1H-pyrazolo[4,3-d]pyrimidine 1-1 with a suitable protecting group (e.g. SEM or Boc). The chloro substituent in the compounds of Formula 1-2 can be converted into Cy<sup>4</sup> via a number of different cross-coupling reactions, including Suzuki (e.g., in the presence of a palladium catalyst, such as Xphos Pd G2, and a base, such as potassium phosphate), Negishi and Stille (e.g., in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine) palladium(0)), Cu-catalyzed amination (e.g., in the presence of Cu catalyst and a ligand, such as CuI and phenanthroline, and a base, such as cesium carbonate or potassium carbonate), and others, to give the compounds of Formula 1-3. Deprotection of the protecting group (e.g., under acidic conditions, such as treatment with HCl or TFA) results in the formation of compounds of Formula 1-4. These compounds can be further halogenated with one of the halogenation agents (e.g., NIS or iodine) to form compounds of Formula 1-5. The NH group of the pyrazole ring of the compounds of Formula 1-5 is protected with a suitable protecting group, such as Boc or SEM, to form compounds of Formula 1-6. The halogen substituent in the compounds of Formula 1-6 can be converted into R<sup>1</sup> via a number of different cross-coupling reactions, including Stille (ACS Catalysis 2015, 5, 3040-3053) Suzuki (Tetrahedron 2002, 58, 9633-9695), Sonogashira (Chem. Soc. Rev. 2011, 40, 5084-5121), Negishi (ACS Catalysis 2016, 6, 1540-1552), Buchwald-Hartwig amination (Chem. Sci. 2011, 2, 27-50), Cu-catalyzed amination (Org. React. 2014, 85, 1-688) and others, to give the compounds of Formula 1-7. Finally, deprotection of the protecting group under acidic conditions (e.g., treatment with HCl or TFA) results in the formation of the desired compounds of Formula (I).



**[0375]** Alternatively, to install various substitutions at position  $Cy^4$ , compounds of Formula (I) can be prepared using a process as illustrated in Scheme 2. Iodination of 5-chloro-1H-pyrazolo[4,3-d]pyrimidine 1-1 with one of the iodination agents, such as iodine or NIS, forms compounds of Formula 2-2. The NH group of the pyrazole ring of the compounds of Formula 2-2 is protected with a suitable protecting group (e.g., Boc or SEM) to form compounds of Formula 2-3. The iodo substituent in the compounds of Formula 2-3 can be converted into  $R^1$  via a number of different cross-coupling reactions, including Suzuki, Sono-

gashira, Negishi, Buchwald-Hartwig amination, Cu-catalyzed amination and others, to give the compounds of Formula 2-4. The chloro substituent in the compounds of Formula 2-4 can be further converted into  $Cy^4$  via a number of different cross-coupling reactions, including Suzuki, Stille, Negishi, Cu-catalyzed amination and others, to give the compounds of Formula 2-5. Finally, deprotection of the protecting group, e.g. under acidic conditions, such as treatment with HCl or TFA, results in the formation of the desired compounds of Formula (I).

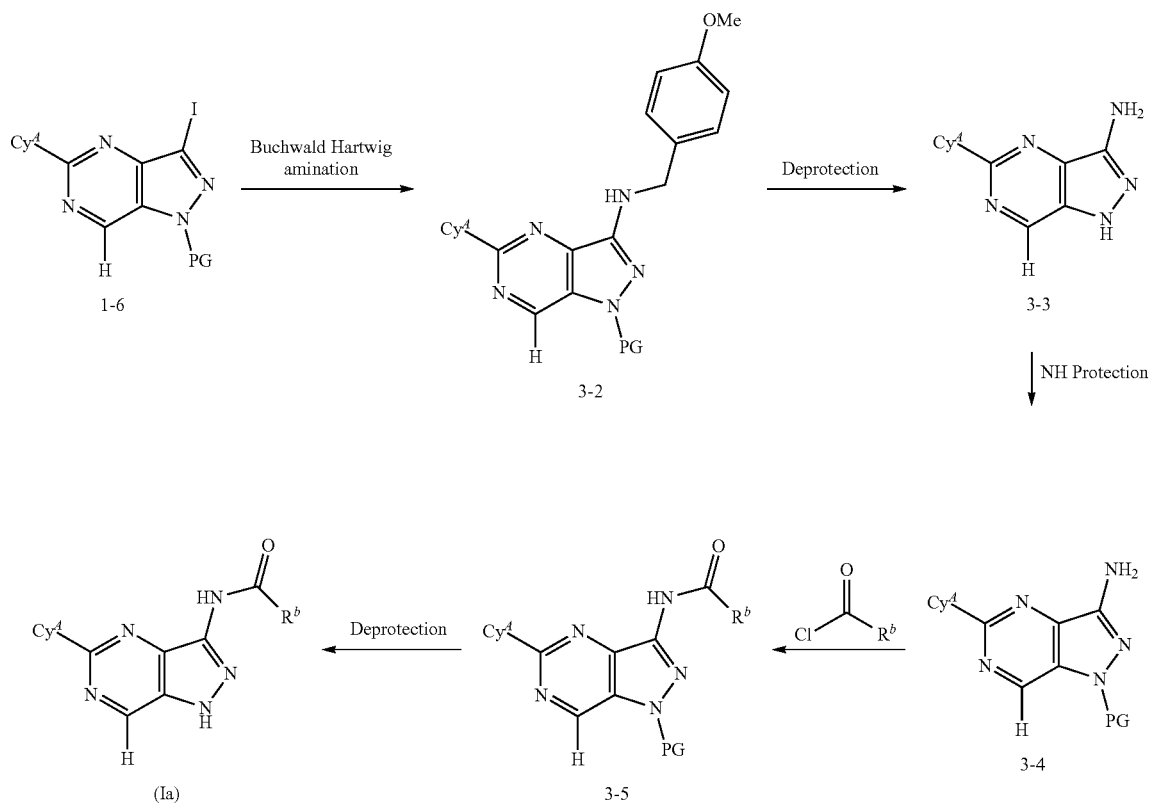




**[0376]** Compounds of Formula (Ia) (compounds of Formula I wherein  $R^1$  is  $NR^cC(O)R^b$ ) can be prepared, using a process as illustrated in Scheme 3. In the process depicted in Scheme 3, compounds of Formula 1-6 reacts with an amine, e.g. (4-methoxyphenyl)methanamine, under standard Buchwald-Hartwig amination conditions (e.g. Pd-catalyst, such as Ruphos Pd G2, and a base, such as cesium carbonate) to form compounds of Formula 3-2. Deprotection of the protecting groups (e.g., under acidic conditions, such as treatment with TFA) results in the formation of compounds of Formula 3-3. The NH group of the pyrazole ring of the

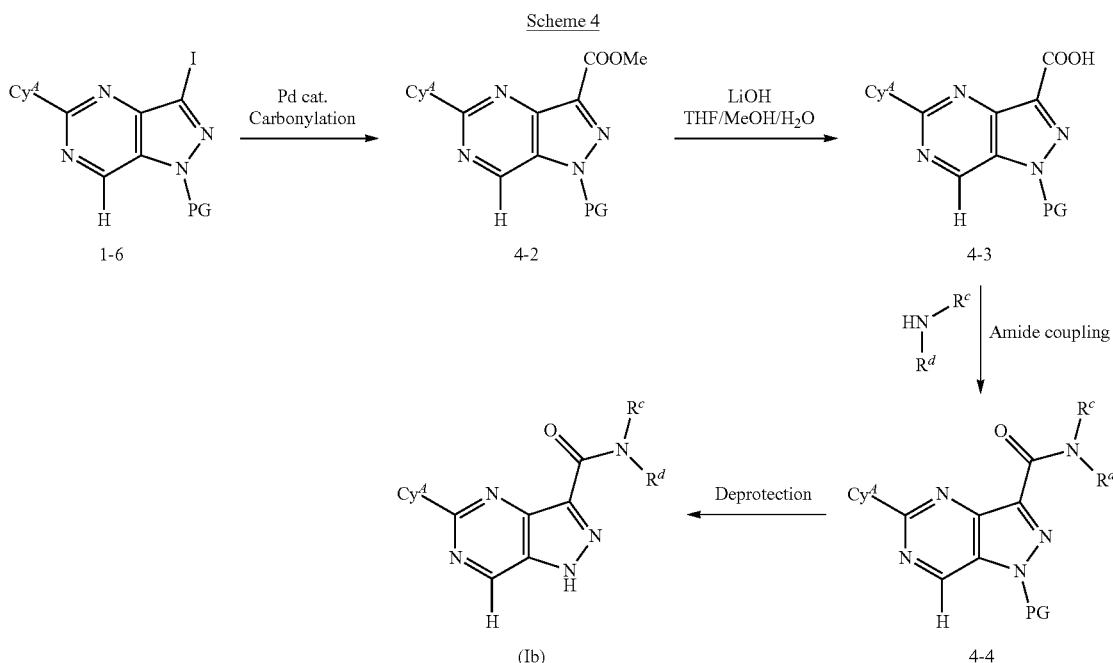
compounds of Formula 3-3 is protected with a suitable protecting group (e.g., Boc) to form compounds of Formula 3-4. Compounds of Formula 3-4 react with different acid chlorides in a presence of base, such as triethylamine or DIPEA, to form compounds of Formula 3-5. Finally, deprotection of the protecting group, e.g. under acidic conditions, such as treatment with HCl or TFA, results in the formation of the desired compounds of Formula (Ia). Alternatively compounds of Formula 3-5 can be alkylated or arylated and then deprotected to prepare amides wherein  $R^c$  is other than hydrogen.

Scheme 3





**[0377]** Compounds of Formula (Ib) (compounds of Formula I wherein  $R^1$  is  $C(O)NR^cR^d$ ) can be prepared, using a process as illustrated in Scheme 4. In the process depicted in Scheme 4, compounds of Formula 1-6 are converted into compounds of formula 4-2 under Pd-catalyzed carbonylation conditions, such as in a presence of Pd catalyst (e.g.,  $Pd(dppf)Cl_2 \cdot DCM$ ) and base (e.g., triethylamine) under carbon monoxide atmosphere. Hydrolysis of the ester group under basic conditions, such as LiOH or NaOH, forms the compounds of Formula 4-3. Compounds of the Formula 4-3 can be coupled to an amine,  $HNR^cR^d$ , using standard amide coupling agents (e.g., HBTU, HATU or EDC) to give compounds of Formula 4-4. Finally, deprotection of the protecting group, e.g. under acidic conditions, such as treatment with HCl or TFA, results in the formation of the desired compounds of Formula (Ib).



#### HPK1 Kinase

**[0378]** Extensive studies have established that HPK1 is a negative regulator of T cell and B cell activation (Hu, M. C., et al., *Genes Dev*, 1996. 10(18): p. 2251-64; Kiefer, F., et al., *EMBO J*, 1996. 15(24): p. 7013-25). HPK1-deficient mouse T cells showed dramatically increased activation of TCR proximal signaling, enhanced IL-2 production, and hyper-proliferation in vitro upon anti-CD3 stimulation (Shui, J. W., et al., *Nat Immunol*, 2007. 8(1): p. 84-91). Similar to T cells, HPK1 knockout B cells produced much higher levels of IgM and IgG isoforms after KLH immunization and displayed hyper-proliferation potentially as a result of enhanced BCR signaling. Wang, X., et al., *J Biol Chem*, 2012. 287(14): p. 11037-48. Mechanistically, during TCR or BCR signaling, HPK1 is activated by LCK/ZAP70 (T cells) or SYK/LYN (B cells) mediated-Tyr379 phosphorylation and its subsequent binding to adaptor protein SLP-76 (T cells) or BLNK (B cells) (Wang, X., et al., *J Biol Chem*, 2012. 287(14): p. 11037-48). Activated HPK1 phosphorylates SLP-76 on

Ser376 or BLNK on Thr152, leading to the recruitment of signaling molecule 14-3-3 and ultimate ubiquitination-mediated degradation of SLP-76 or BLNK (Liou, J., et al., *Immunity*, 2000. 12(4): p. 399-408; Di Bartolo, V., et al., *J Exp Med*, 2007. 204(3): p. 681-91). As SLP-76 and BLNK are essential for TCR/BCR-mediated signaling activation (e.g. ERK, phospholipase  $Cy1$ , calcium flux, and NFAT activation), HPK1-mediated downregulation of these adaptor proteins provide a negative feedback mechanism to attenuate signaling intensity during T cell or B cell activation (Wang, X., et al., *J Biol Chem*, 2012. 287(14): p. 11037-48).

**[0379]** The bone marrow-derived dendritic cells (BDMCs) from HPK1 knockout mice showed higher expression of co-stimulatory molecules (e.g. CD80/CD86) and enhanced production of proinflammatory cytokines (IL-12, TNF- $\alpha$

etc), and demonstrated superior ability to stimulate T cell proliferation in vitro and in vivo as compared to wild-type DCs (Alzabin, S., et al., *J Immunol*, 2009. 182(10): p. 6187-94). These data suggest that HPK1 is also an important negative regulator of dendritic cell activation (Alzabin, S., et al., *J Immunol*, 2009. 182(10): p. 6187-94). However, the signaling mechanisms underlying HPK-1 mediated negative regulation of DC activation remains to be elucidated.

**[0380]** In contrast, HPK1 appears to be a positive regulator of suppressive functions of regulatory T cells (Treg) (Sawasdikosol, S. et al., *The journal of immunology*, 2012. 188(supplement 1): p. 163). HPK1 deficient mouse Foxp3+ Tregs were defective in suppressing TCR-induced effector T cell proliferation, and paradoxically gained the ability to produce IL-2 following TCR engagement (Sawasdikosol, S. et al., *The Journal of Immunology*, 2012. 188(supplement 1): p. 163). These data suggest that HPK1 is an important regulator of Treg functions and peripheral self-tolerance.

**[0381]** HPK1 was also involved in PGE2-mediated inhibition of CD4+ T cell activation (Ikegami, R., et al., *J*

Immunol. 2001. 166(7): p. 4689-96). Studies published in US 2007/0087988 indicated that HPK1 kinase activity was increased by exposure to physiological concentrations of PGE2 in CD4+ T cells and this effect was mediated by PEG2-induced PKA activation. The proliferation of HPK1 deficient T cells was resistant to the suppressive effects of PGE2 (see US 2007/0087988). Therefore, PGE2-mediated activation of HPK1 may represent a novel regulatory pathway of modulating immune response.

**[0382]** The present disclosure provides methods of modulating (e.g., inhibiting) HPK1 activity, said method comprising administering to a patient a compound provided herein, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compounds of the present disclosure, or pharmaceutically acceptable salts thereof, are useful for therapeutic administration to enhance, stimulate and/or increase immunity in cancer. For example, a method of treating a disease or disorder associated with inhibition of HPK1 interaction can include administering to a patient in need thereof a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof. The compounds of the present disclosure can be used alone, in combination with other agents or therapies or as an adjuvant or neoadjuvant for the treatment of diseases or disorders, including cancers. For the uses described herein, any of the compounds of the disclosure, including any of the embodiments thereof, may be used.

**[0383]** Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, endometrial cancer, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

**[0384]** In some embodiments, cancers treatable with compounds of the present disclosure include melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer, triple-negative breast cancer, colon cancer and lung cancer (e.g. non-small cell lung cancer and small cell lung cancer). Additionally, the disclosure includes refractory or recurrent malignancies whose growth may be inhibited using the compounds of the disclosure.

**[0385]** In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but

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

**[0386]** In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

**[0387]** Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocythosis (ET)), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL), multiple myeloma, cutaneous T-cell lymphoma, Waldenstrom's Macroglobulinemia, hairy cell lymphoma, chronic myelogenous lymphoma and Burkitt's lymphoma.

**[0388]** Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, hamartoma, and teratoma.

**[0389]** Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

**[0390]** Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer.

**[0391]** Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, chorio-carcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

**[0392]** Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

**[0393]** Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

**[0394]** Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

**[0395]** Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

**[0396]** Exemplary skin cancers include melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, Merkel cell skin cancer, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids. In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to, sickle cell disease (e.g., sickle cell anemia), triple-negative breast cancer (TNBC), myelodysplastic syndromes, testicular cancer, bile duct cancer, esophageal cancer, and urothelial carcinoma.

**[0397]** Exemplary head and neck cancers include glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, osteosarcoma, squamous cell carcinomas, adenocarcinomas, oral cancer, laryngeal cancer, nasopharyngeal cancer, nasal and paranasal cancers, thyroid and parathyroid cancers.

**[0398]** In some embodiments, HPK1 inhibitors may be used to treat tumors producing PGE2 (e.g. Cox-2 overexpressing tumors) and/or adenosine (CD73 and CD39 overexpressing tumors). Overexpression of Cox-2 has been detected in a number of tumors, such as colorectal, breast, pancreatic and lung cancers, where it correlates with a poor prognosis. Overexpression of COX-2 has been reported in hematological cancer models such as RAJI (Burkitt's lymphoma) and U937 (acute promonocytic leukemia) as well as in patient's blast cells. CD73 is up-regulated in various human carcinomas including those of colon, lung, pancreas and ovary. Importantly, higher expression levels of CD73 are associated with tumor neovascularization, invasiveness, and metastasis and with shorter patient survival time in breast cancer.

**[0399]** The terms "individual" or "patient," used interchangeably, refer to any animal, including mammals, pref-

erably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

**[0400]** The phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

**[0401]** As used herein, the term "treating" or "treatment" refers to one or more of (1) inhibiting the disease; e.g., inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (2) ameliorating the disease; e.g., ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

**[0402]** In some embodiments, the compounds of the invention are useful in preventing or reducing the risk of developing any of the diseases referred to herein; e.g., preventing or reducing the risk of developing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

#### Combination Therapies

**[0403]** Cancer cell growth and survival can be impacted by multiple signaling pathways. Thus, it is useful to combine different enzyme/protein/receptor inhibitors, exhibiting different preferences in the targets which they modulate the activities of, to treat such conditions. Examples of agents that may be combined with compounds of the present disclosure include inhibitors of the PI3K-AKT-mTOR pathway, inhibitors of the Raf-MAPK pathway, inhibitors of JAK-STAT pathway, inhibitors of beta catenin pathway, inhibitors of notch pathway, inhibitors of hedgehog pathway, inhibitors of Pim kinases, and inhibitors of protein chaperones and cell cycle progression. Targeting more than one signaling pathway (or more than one biological molecule involved in a given signaling pathway) may reduce the likelihood of drug-resistance arising in a cell population, and/or reduce the toxicity of treatment.

**[0404]** The compounds of the present disclosure can be used in combination with one or more other enzyme/protein/receptor inhibitors for the treatment of diseases, such as cancer. Examples of cancers include solid tumors and liquid tumors, such as blood cancers. For example, the compounds of the present disclosure can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, TGF- $\beta$ R, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IGF-1R, IR-R, PDGF $\alpha$ R, PDGF $\beta$ R, CSFIR, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, Ron, Sea, TRKA, TRKB, TRKC, FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. In some embodiments, the compounds of the present disclosure can be combined with one or more of the following

inhibitors for the treatment of cancer. Non-limiting examples of inhibitors that can be combined with the compounds of the present disclosure for treatment of cancers include an FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, e.g., AZD4547, BAY1187982, ARQ087, BGJ398, BIBF1120, TKI258, lucitanib, dovitinib, TAS-120, JNJ-42756493, Debio1347, INCB54828, INCB62079 and INCB63904), a JAK inhibitor (JAK1 and/or JAK2, e.g., ruxolitinib, baricitinib or INCB39110), an IDO inhibitor (e.g., epacadostat and NLG919), an LSD1 inhibitor (e.g., GSK2979552, INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor (e.g., INCB50797 and INCB50465), a PI3K-gamma inhibitor such as a PI3K-gamma selective inhibitor, a CSF1R inhibitor (e.g., PLX3397 and LY3022855), a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer), an angiogenesis inhibitor, an interleukin receptor inhibitor, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors such as OTX015, CPI-0610, INCB54329 and INCB57643) and an adenosine receptor antagonist or combinations thereof. Inhibitors of HDAC such as panobinostat and vorinostat. Inhibitors of c-Met such as onartumzumab, tivantinib, and INC-280. Inhibitors of BTK such as ibrutinib. Inhibitors of mTOR such as rapamycin, sirolimus, temsirolimus, and everolimus. Inhibitors of Raf, such as vemurafenib and dabrafenib. Inhibitors of MEK such as trametinib, selumetinib and GDC-0973. Inhibitors of Hsp90 (e.g., tanespimycin), cyclin dependent kinases (e.g., palbociclib), PARP (e.g., olaparib) and Pim kinases (LGH447, INCB053914 and SGI-1776) can also be combined with compounds of the present disclosure.

**[0405]** Compounds of the present disclosure can be used in combination with one or more immune checkpoint inhibitors. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CD20, CD27, CD28, CD39, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TIGR beta inhibitors.

**[0406]** In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

**[0407]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD1 antibody is pembrolizumab. In some embodiments, the anti PD-1 antibody is SHR-1210.

**[0408]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A or MEDI4736.

**[0409]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab.

**[0410]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CSF1R, e.g., an anti-CSF1R antibody. In some embodiments, the anti-CSF1R antibody is IMC-CS4 or RG7155.

**[0411]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016, LAG525, IMP321 or GSK2831781.

**[0412]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX518, MK-4166, MK1248, BMS-986156, MEDI1873 or GWN323.

**[0413]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of OX40, e.g., an anti-OX40 antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562, MEDI6469, MOXR0916, PF-04518600 or GSK3174998. In some embodiments, the OX40L fusion protein is MEDI6383.

**[0414]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIM3, e.g., an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is MBG-453.

**[0415]** In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD20, e.g., an anti-CD20 antibody. In some embodiments, the anti-CD20 antibody is obinutuzumab or rituximab.

**[0416]** In some embodiments, the compounds of the invention can be used in combination with one or more metabolic enzyme inhibitors. In some embodiments, the metabolic enzyme inhibitor is an inhibitor of IDO1, TDO, or arginase. Examples of IDO1 inhibitors include epacadostat and NGL919. An example of an arginase inhibitor is CB-1158.

**[0417]** The compounds of the present disclosure can be used in combination with bispecific antibodies. In some embodiments, one of the domains of the bispecific antibody targets PD-1, PD-L1, CTLA-4, GITR, OX40, TIM3, LAG3, CD137, ICOS, CD3 or TGF $\beta$  receptor.

**[0418]** Compounds of the present disclosure can be used in combination with one or more agents for the treatment of diseases such as cancer. In some embodiments, the agent is an alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include bendamustine, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes, uracil mustard, chlormethine, cyclophosphamide (Cytosan<sup>TM</sup>), ifosfamide, melphalan, chlorambucil, pipobroman, triethylene-melamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, and temozolomide. In some embodiments, the proteasome

inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM).

**[0419]** The compounds of the present disclosure can further be used in combination with other methods of treating cancers, for example by chemotherapy, irradiation therapy, tumor-targeted therapy, adjuvant therapy, immunotherapy or surgery. Examples of immunotherapy include cytokine treatment (e.g., interferons, GM-CSF, G-CSF, IL-2), CRS-207 immunotherapy, cancer vaccine, monoclonal antibody, adoptive T cell transfer, oncolytic virotherapy and immunomodulating small molecules, including thalidomide or JAK1/2 inhibitor and the like. The compounds can be administered in combination with one or more anti-cancer drugs, such as a chemotherapeutics. Example chemotherapeutics include any of: abarelix, abiraterone, afatinib, aflibercept, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, axitinib, azacitidine, bevacizumab, bexarotene, baricitinib, bicalutamide, bleomycin, bortezomib, bortezomib, brivanib, buparlisib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cediranib, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, crizotinib, cyclophosphamide, cytarabine, dacarbazine, dacomitinib, dactinomycin, dalteparin sodium, dasatinib, dactinomycin, daunorubicin, decitabine, degarelix, denileukin, denileukin difitox, deoxycorformycin, dexrazoxane, docetaxel, doxorubicin, droloxafine, dromostanolone propionate, eculizumab, enzalutamide, epidophyllotoxin, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, flutamide, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, idelalisib, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, meclizethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mithramycin, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, navelbine, necitumumab, nelarabine, neratinib, nilotinib, nilutamide, nefe-tumomab, oserelin, oxaliplatin, paclitaxel, pamidronate, panitumumab, pazopanib, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pilaralisib, pipobroman, plicamycin, ponatinib, prednisone, procarbazine, quina-crine, rasburicase, regorafenib, reloxafine, rituximab, rux-olitinib, sorafenib, streptozocin, sunitinib maleate, tamoxifen, tegafur, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, triptorelin, uracil must-tard, valrubicin, vandetanib, vinblastine, vincristine, vinore-bine, vorinostat and zoledronate.

**[0420]** Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4 (e.g., ipilimumab or tremelimumab), 4-1BB, antibodies to PD-1 and PD-L1, or antibodies to cytokines (IL-10, TGF- $\beta$ , etc.). Examples of antibodies to PD-1 and/or PD-L1 that can be combined with compounds of the present disclosure for the treatment of cancer or infections such as viral, bacteria, fungus and parasite infections include, but are not limited to, nivolumab, pembrolizumab, MPDL3280A, MEDI-4736 and SHR-1210.

**[0421]** Other anti-cancer agents include inhibitors of kinases associated cell proliferative disorder. These kinases include but not limited to Aurora-A, CDK1, CDK2, CDK3, CDK5, CDK7, CDK8, CDK9, ephrin receptor kinases, CHK1, CHK2, SRC, Yes, Fyn, Lck, Fer, Fes, Syk, Itk, Bmx, GSK3, JNK, PAK1, PAK2, PAK3, PAK4, PDK1, PKA, PKC, Rsk and SGK.

**[0422]** Other anti-cancer agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4.

**[0423]** The compounds of the present disclosure can further be used in combination with one or more anti-inflammatory agents, steroids, immunosuppressants or therapeutic antibodies.

**[0424]** The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with another immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MARTI and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

**[0425]** The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to express GM-CSF. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). In some embodiments, the compounds of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated from tumor tissue itself. In some embodiments, the compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with dendritic cells immunization to activate potent anti-tumor responses.

**[0426]** The compounds of the present disclosure can be used in combination with bispecific macrocyclic peptides that target Fe alpha or Fe gamma receptor-expressing effectors cells to tumor cells. The compounds of the present disclosure can also be combined with macrocyclic peptides that activate host immune responsiveness.

**[0427]** The compounds of the present disclosure can be used in combination with bone marrow transplant for the treatment of a variety of tumors of hematopoietic origin.

**[0428]** Suitable antiviral agents contemplated for use in combination with the compounds of the present disclosure can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and other antiviral drugs.

**[0429]** Example suitable NRTIs include zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil [bis(POM)-PMEA]; lobucavir (BMS-180194); BCH-10652; emtricitabine [(-)-FTC]; beta-L-FD4 (also called beta-L-

D4C and named beta-L-2',3'-dideoxy-5-fluoro-cytidine); DAPD, ((-)-beta-D-2,6,-diamino-purine dioxolane); and lodenosine (FddA). Typical suitable NNRTIs include nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4 (1H,3H)-pyrimidinedione); and (+)-calanolide A (NSC-675451) and B. Typical suitable protease inhibitors include saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfinavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; and AG-1 549. Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No. 11607.

**[0430]** When more than one pharmaceutical agent is administered to a patient, they can be administered simultaneously, separately, sequentially, or in combination (e.g., for more than two agents).

#### Formulation, Dosage Forms and Administration

**[0431]** When employed as pharmaceuticals, the compounds of the present disclosure can be administered in the form of pharmaceutical compositions. Thus the present disclosure provides a composition comprising a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt thereof, or any of the embodiments thereof, and at least one pharmaceutically acceptable carrier or excipient. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is indicated and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, e.g., by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

**[0432]** This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the present disclosure or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, e.g., a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions,

syrups, aerosols (as a solid or in a liquid medium), ointments containing, e.g., up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

**[0433]** 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.

**[0434]** The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art see, e.g., WO 2002/000196.

**[0435]** Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

**[0436]** In some embodiments, the pharmaceutical composition comprises silicified microcrystalline cellulose (SMCC) and at least one compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the silicified microcrystalline cellulose comprises about 98% microcrystalline cellulose and about 2% silicon dioxide w/w.

**[0437]** In some embodiments, the composition is a sustained release composition comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose and polyethylene oxide. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and polyethylene oxide. In some embodiments, the composition further comprises magnesium stearate or silicon dioxide. In some embodiments, the microcrystalline cellulose is Avicel PH102™. In some embodiments, the lactose monohydrate is Fast-flo 316™. In some embodiments, the hydroxypropyl methylcellulose is hydroxypropyl methylcellulose 2208 K4M (e.g., Methocel K4 M Premier™) and/or hydroxypropyl methylcellulose

2208 K100LV (e.g., Methocel K00LV™). In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (e.g., Polyox WSR 1105™).

**[0438]** In some embodiments, a wet granulation process is used to produce the composition. In some embodiments, a dry granulation process is used to produce the composition.

**[0439]** The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. In some embodiments, each dosage contains about 10 mg of the active ingredient. In some embodiments, each dosage contains about 50 mg of the active ingredient. In some embodiments, each dosage contains about 25 mg of the active ingredient. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

**[0440]** The components used to formulate the pharmaceutical compositions are of high purity and are substantially free of potentially harmful contaminants (e.g., at least National Food grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Particularly for human consumption, the composition is preferably manufactured or formulated under Good Manufacturing Practice standards as defined in the applicable regulations of the U.S. Food and Drug Administration. For example, suitable formulations may be sterile and/or substantially isotonic and/or in full compliance with all Good Manufacturing Practice regulations of the U.S. Food and Drug Administration.

**[0441]** The active compound may be effective over a wide dosage range and is generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the like.

**[0442]** The therapeutic dosage of a compound of the present invention can vary according to, e.g., the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

**[0443]** For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, e.g., about 0.1 to about 1000 mg of the active ingredient of the present invention.

**[0444]** 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.

**[0445]** 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.

**[0446]** Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

**[0447]** Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, e.g., liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g., glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, e.g., glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2 or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, e.g., 100 g which are option-

ally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

**[0448]** The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient and the like.

**[0449]** The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers or stabilizers will result in the formation of pharmaceutical salts.

**[0450]** The therapeutic dosage of a compound of the present invention can vary according to, e.g., the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

#### Labeled Compounds and Assay Methods

**[0451]** The compounds of the present disclosure can further be useful in investigations of biological processes in normal and abnormal tissues. Thus, another aspect of the present invention relates to fluorescent dye, spin label, heavy metal or radio-labeled compounds provided herein that would be useful not only in imaging techniques but also in assays, both in vitro and in vivo, for localizing and quantitating HPK1 protein in tissue samples, including human, and for identifying HPK1 ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes HPK1 binding assays that contain such labeled compounds.

**[0452]** The present invention further includes isotopically-substituted compounds of the disclosure. An “isotopically-substituted” compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having the same atomic number but a different atomic mass or mass number. Compounds of the invention may contain isotopes in a natural abundance as found in nature. Compounds of the invention may also have isotopes in amounts greater to that found in nature, e.g., synthetically incorporating low natural abundance isotopes into the compounds of the invention so they are enriched in a particularly useful isotope (e.g.,  $^2\text{H}$  and  $^{13}\text{C}$ ). It is to be understood that a “radio-labeled” compound is a compound that has incorporated at least one isotope that is radioactive (e.g., radionuclide), e.g.,  $^3\text{H}$  and  $^{14}\text{C}$ . Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to  $^3\text{H}$  (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. In some embodiments, the radionuclide is selected from the group consisting of  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{125}\text{I}$ ,  $^{35}\text{S}$  and  $^{82}\text{Br}$ . For in vitro HPK1 labeling and competition assays, compounds that incorporate  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{82}\text{Br}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ , or  $^{35}\text{S}$  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. Synthetic methods for incorporating radio-isotopes into organic compounds are known in the art.

**[0453]** Specifically, a labeled compound of the invention can be used in a screening assay to identify and/or evaluate compounds. For example, a newly synthesized or identified compound (i.e., test compound) which is labeled can be evaluated for its ability to bind a HPK1 protein by monitoring its concentration variation when contacting with the HPK1, 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 HPK1 protein (i.e., standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the HPK1 protein directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

#### Kits

**[0454]** The present disclosure also includes pharmaceutical kits useful, e.g., in the treatment or prevention of diseases or disorders associated with the activity of HPK1, such as cancer or infections, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, e.g., containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for



administration, and/or guidelines for mixing the components, can also be included in the kit.

**[0455]** The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to inhibit the activity of HPK1 according to at least one assay described herein.

#### EXAMPLES

**[0456]** Experimental procedures for compounds of the invention are provided below. Preparatory LC-MS purifications of some of the compounds prepared were performed on Waters mass directed fractionation systems. The basic equipment setup, protocols, and control software for the operation of these systems have been described in detail in the literature. See e.g. "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Comb. Chem.*, 4, 295 (2002); "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", K. Blom, R. Sparks, J. Doughty, G. Everlof, T. Hague, A. Combs, *J. Comb. Chem.*, 5, 670 (2003); and "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, 6, 874-883 (2004). The compounds separated were typically subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity check under the following conditions: Instrument; Agilent 1100 series, LC/MSD, Column: Waters Sunfire™ C<sub>18</sub> 5 μm particle size, 2.1×5.0 mm, Buffers: mobile phase A: 0.025% TFA in water and mobile phase B: acetonitrile; gradient 2% to 80% of B in 3 minutes with flow rate 2.0 mL/minute.

**[0457]** Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-phase high performance liquid chromatography (RP-HPLC) column conditions are as follows:

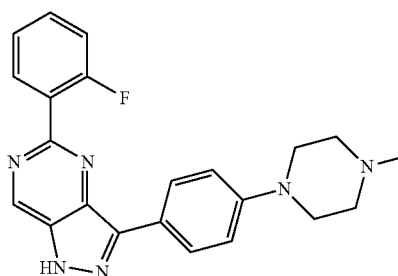
**[0458]** pH=2 purifications: Waters Sunfire™ C<sub>18</sub> 5 μm particle size, 19×100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [see "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, 6, 874-883 (2004)]. Typically, the flow rate used with the 30×100 mm column was 60 mL/minute.

**[0459]** pH=10 purifications: Waters XBridge C<sub>18</sub> 5 μm particle size, 19×100 mm column, eluting with mobile phase A: 0.15% NH<sub>4</sub>OH in water and mobile phase B: acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [See "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, 6, 874-883 (2004)]. Typically, the flow rate used with 30×100 mm column was 60 mL/minute.

#### Example 1

5-(2-Fluorophenyl)-3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazolo[4,3-d]pyrimidine

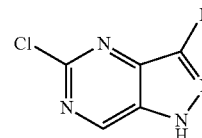
**[0460]**



#### Step 1.

5-Chloro-3-iodo-1H-pyrazolo[4,3-c]pyrimidine

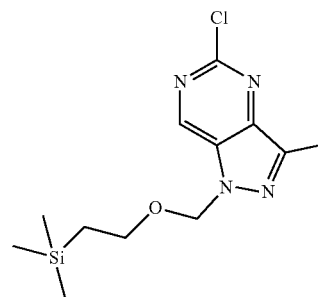
**[0461]**



**[0462]** Potassium hydroxide (2.2 g, 39 mmol) and iodine (4.9 g, 19 mmol) were added to a solution of 5-chloro-1H-pyrazolo[4,3-d]pyrimidine (Astatech, 1.5 g, 9.7 mmol) in 1,4-dioxane (20 mL). The reaction mixture was stirred at 50° C. for 2 hours. After cooling to r.t., water was added and the reaction was neutralized to pH 7. The mixture was then extracted with ethyl acetate and the organic phase was washed with brine. The organic phase was dried over sodium sulfate and the solvents were evaporated under reduced pressure. The crude product was purified by Biotage Isolera™ (1 g, 37%). LCMS calculated for C<sub>5</sub>H<sub>3</sub>ClIN<sub>4</sub> (M+H)<sup>+</sup> m/z=280.9; found 281.0.

Step 2. 5-Chloro-3-iodo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazolo[4,3-d]pyrimidine

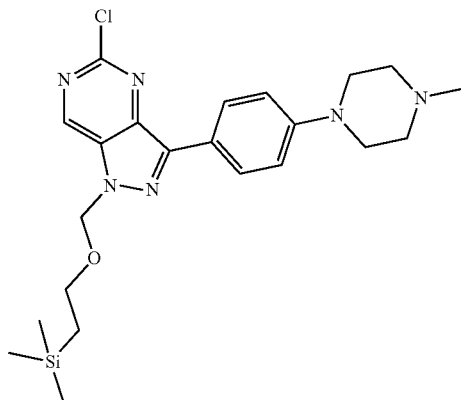
**[0463]**



**[0464]** NaH in mineral oil (150 mg, 3.8 mmol) was slowly added at 0° C. to a solution of 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine (964 mg, 3.44 mmol) and [ $\beta$ -(trimethylsilyl)ethoxy]methyl chloride (639  $\mu$ L, 3.61 mmol) in tetrahydrofuran (10 mL). After stirring at r.t. for 1 h, the reaction mixture was quenched by the addition of water and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried over sodium sulfate. The solvents were evaporated under reduced pressure and the crude product was purified by Biotage Isolera™ (1.2 g, 88%). LCMS calculated for  $C_{11}H_{17}ClN_4OSi$  (M+H)<sup>+</sup> m/z=411.0; found 411.0.

Step 3. 5-Chloro-3-[4-(4-methylpiperazin-1-yl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine

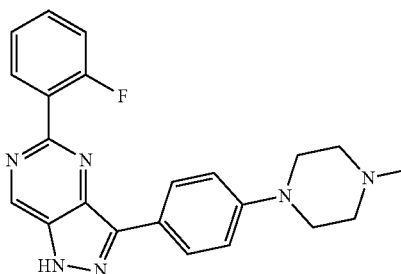
**[0465]**



**[0466]** 5-Chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine (636 mg, 1.55 mmol), [4-(4-methylpiperazin-1-yl)phenyl]boronic acid (340 mg, 1.5 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complexed with dichloromethane (1:1) (100 mg, 0.2 mmol), potassium phosphate (430 mg, 2.0 mmol) and a magnet bar were placed in a vial. The vial was sealed with a Teflon screw-cap, evacuated and backfilled with nitrogen (this process was repeated a total of three times). After dioxane (12 mL) and degassed water (2 mL) were added, the mixture was heated at 100° C. for 16 h. The reaction mixture was then diluted with ethyl acetate, washed with brine and dried over sodium sulfate. The solvents were evaporated under reduced pressure and the crude product was purified by Biotage Isolera™ (520 mg, 74%). LCMS calculated for  $C_{22}H_{32}ClN_6OSi$  (M+H)<sup>+</sup> m/z=459.2; found 459.3.

Step 4. 5-(2-Fluorophenyl)-3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazolo[4,3-d]pyrimidine

**[0467]**

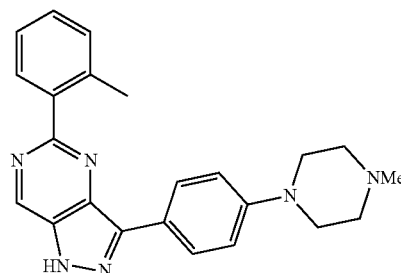


**[0468]** 5-Chloro-3-[4-(4-methylpiperazin-1-yl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine (15 mg, 0.033 mmol), (2-fluorophenyl)boronic acid (6.8 mg, 0.049 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (Pd XPhos G2) (2.6 mg, 0.0033 mmol), potassium phosphate (21 mg, 0.098 mmol) and a magnet bar were placed in a vial with septum which was then evacuated and backfilled with nitrogen three times. 1,4-Dioxane (2.5 mL) and degassed water (0.3 mL) were added and the reaction mixture was stirred at 80° C. for 1 h. Then 1M solution of HCl in water (1 mL) and 4M solution of HCl in dioxane (1 mL) were added and reaction was stirred at 80° C. for 1 h. Methanol (1 mL) was added and reaction was further stirred at 80° C. for 30 min. The reaction mixture was then diluted with acetonitrile and was purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS calculated for  $C_{22}H_{22}FN_6$  (M+H)<sup>+</sup>: m/z=389.2; Found: 389.3.

## Example 2

3-(4-(4-Methylpiperazin-1-yl)phenyl)-5-o-tolyl-1H-pyrazolo[4,3-d]pyrimidine

**[0469]**

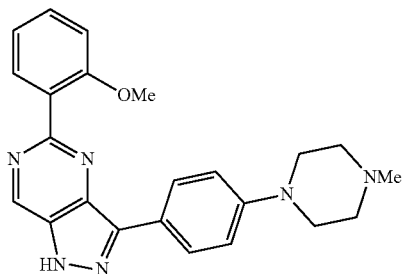


**[0470]** This compound was prepared according to the procedures described in Example 1, using o-tolylboronic acid, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{23}H_{25}N_6$  (M+H)<sup>+</sup>: m/z=385.2; Found: 385.3.

## Example 3

5-(2-Methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0471]

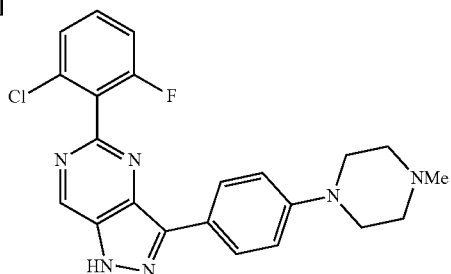


[0472] This compound was prepared according to the procedures described in Example 1, using 2-methoxyphenylboronic acid, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{23}H_{25}N_6O$  (M+H)<sup>+</sup>: m/z=401.2; Found: 401.3.

## Example 4

5-(2-Chloro-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0473]

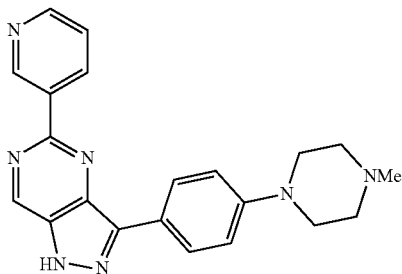


[0474] This compound was prepared according to the procedures described in Example 1, using 2-chloro-6-fluorophenylboronic acid, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{22}H_{21}ClFN_6$  (M+H)<sup>+</sup>: m/z=423.2; Found: 423.2.

## Example 5

3-(4-(4-Methylpiperazin-1-yl)phenyl)-5-(pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0475]

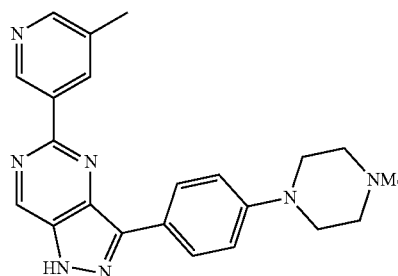


[0476] This compound was prepared according to the procedures described in Example 1, using pyridin-3-ylboronic acid, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{21}H_{22}N_7$  (M+H)<sup>+</sup>: m/z=372.2; Found: 372.3.

## Example 6

3-(4-(4-Methylpiperazin-1-yl)phenyl)-5-(5-methylpyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0477]

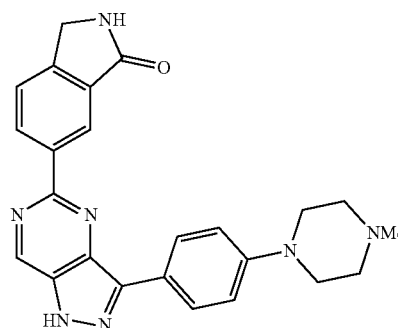


[0478] This compound was prepared according to the procedures described in Example 1, using 5-methylpyridin-3-ylboronic acid, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{22}H_{24}N_7$  (M+H)<sup>+</sup>: m/z=386.2; Found: 386.2.

## Example 7

6-(3-(4-(4-Methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)isoindolin-1-one

[0479]

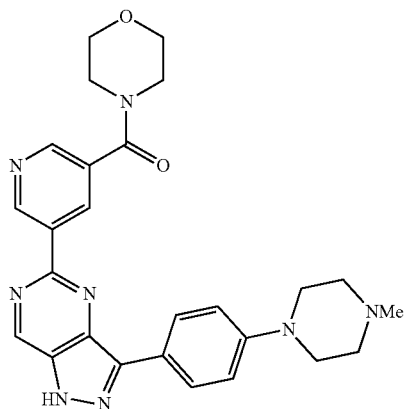


[0480] This compound was prepared according to the procedures described in Example 1, using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{24}H_{24}N_7O$  (M+H)<sup>+</sup>: m/z=426.2; Found: 426.2.

## Example 8

(5-(3-(4-(4-Methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-3-yl)(morpholino) methanone

[0481]

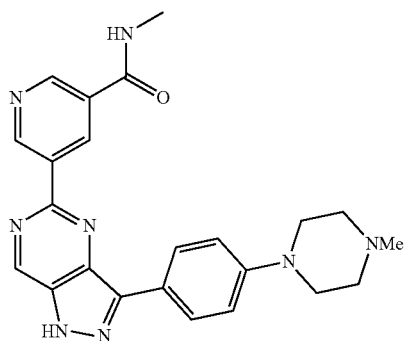


[0482] This compound was prepared according to the procedures described in Example 1, using morpholino(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl) methanone, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{26}H_{29}N_8O_2$  (M+H)<sup>+</sup>: m/z=485.2; Found: 485.2.

## Example 9

N-Methyl-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)nicotinamide

[0483]

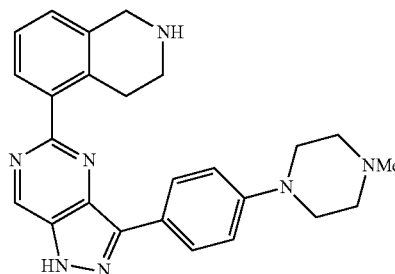


[0484] This compound was prepared according to the procedures described in Example 1, using N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{23}H_{25}N_8O$  (M+H)<sup>+</sup>: m/z=429.2; Found: 429.3.

## Example 10

5-(3-(4-(4-Methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0485]

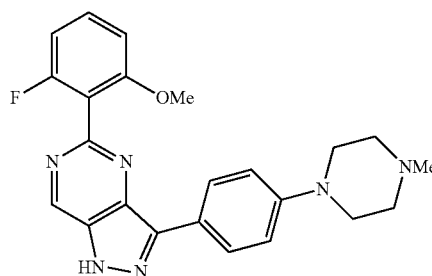


[0486] This compound was prepared according to the procedures described in Example 1, using tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{25}H_{28}N_7$  (M+H)<sup>+</sup>: m/z=426.2; Found: 426.2.

## Example 11

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0487]

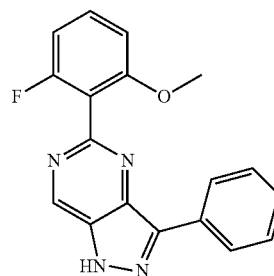


[0488] This compound was prepared according to the procedures described in Example 1, using 2-fluoro-6-methoxyphenylboronic acid, instead of (2-fluorophenyl)boronic acid as starting material. LCMS calculated for  $C_{23}H_{24}FN_6O$  (M+H)<sup>+</sup>: m/z=419.2; Found: 419.3.

## Example 12

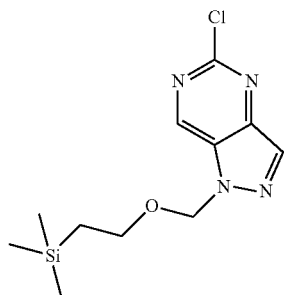
5-(2-Fluoro-6-methoxyphenyl)-3-phenyl-1H-pyrazolo[4,3-d]pyrimidine

[0489]



Step 1. 5-Chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine

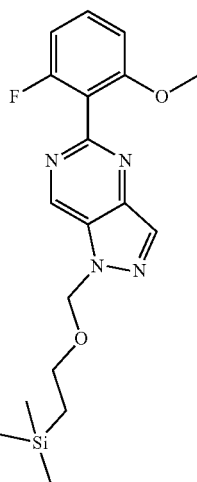
[0490]



[0491] NaH in mineral oil (570 mg, 14 mmol) was slowly added at 0° C. to a solution of 5-chloro-1H-pyrazolo[4,3-d]pyrimidine (2.0 g, 13 mmol) and [ $\beta$ -(trimethylsilyl)ethoxy]methyl chloride (2.40 mL, 13.6 mmol) in tetrahydrofuran (25 mL). After stirring at r.t. for 1 h, the reaction mixture was quenched by the addition of water and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried over sodium sulfate. The solvents were evaporated under reduced pressure and the crude product was purified by Biotage Isolera™ (2.36 g, 64%). LCMS calculated for  $C_{11}H_{18}ClN_4OSi$  (M+H)<sup>+</sup> m/z=285.1; found 285.2.

Step 2. 5-(2-Fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine

[0492]

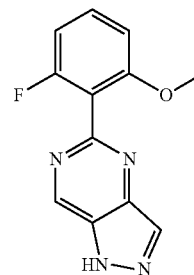


[0493] 5-Chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine (2.36 g, 8.29 mmol), (2-fluoro-6-methoxyphenyl)boronic acid (2.1 g, 12 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-trisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (Pd XPhos G2) (400 mg, 0.5 mmol), potassium phosphate (3.6 g, 17 mmol) and a magnet bar were placed in a flask. The

flask was sealed with a rubber cap, evacuated and backfilled with nitrogen (this process was repeated a total of three times). After dioxane (20 mL) and degassed water (2 mL) were added, the mixture was heated at 90° C. for 1 h. The reaction mixture was then diluted with ethyl acetate, washed with brine and dried over sodium sulfate. The solvents were evaporated under reduced pressure and the crude product was purified by Biotage Isolera™ (3.27 g, 99%). LCMS calculated for  $C_{18}H_{24}FN_4O_2Si$  (M+H)<sup>+</sup> m/z=375.2; found 375.2.

Step 3. 5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine

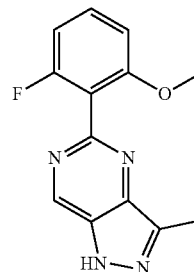
[0494]



[0495] A solution of 5-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine (3.27 g, 8.73 mmol) in a mixture of 1.0 M solution of hydrogen chloride in water (10 mL, 10 mmol) and 4.0 M solution of hydrogen chloride in dioxane (10 mL, 42 mmol) was stirred at 80° C. for 1 h. Then methanol (10 mL) was added and the reaction mixture was further stirred at 80° C. for 30 min. After cooling to r.t., the reaction was neutralized to pH 7. The product was then extracted with ethyl acetate and the organic phase was washed with brine. The organic phase was dried over sodium sulfate and the solvents were evaporated under reduced pressure. The crude product was used in the next step without further purification. LCMS calculated for  $C_{12}H_{10}FN_4O$  (M+H)<sup>+</sup> m/z=245.1; found 245.2.

Step 4. 5-(2-Fluoro-6-methoxyphenyl)-3-iodo-1H-pyrazolo[4,3-d]pyrimidine

[0496]

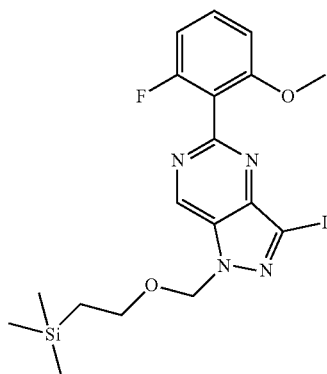


[0497] Potassium hydroxide (2.2 g, 39 mmol) and iodine (4.9 g, 19 mmol) were added to a solution of 5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine (from

previous step) in 1,4-dioxane (20 mL). The reaction mixture was stirred at 50° C. for 2 hours. After cooling to r.t., water was added and reaction was neutralized to pH 7. The product was then extracted with ethyl acetate and the organic phase was washed with a saturated solution of sodium thiosulfate and brine. The organic phase was dried over sodium sulfate and the solvents were evaporated under reduced pressure. The crude product was used in the next step without further purification. LCMS calculated for  $C_{12}H_9FIN_4O$  (M+H)<sup>+</sup> m/z=371.0; found 371.1.

Step 5. 5-(2-Fluoro-6-methoxyphenyl)-3-iodo-1-{{2-(trimethylsilyl)ethoxy)methyl}}-1H-pyrazolo[4,3-d]pyrimidine

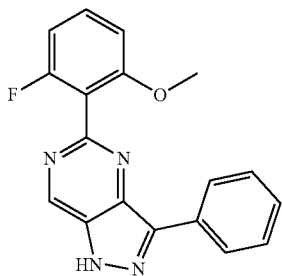
[0498]



[0499] NaH in mineral oil (470 mg, 12 mmol) was slowly added at 0° C. to a solution of 5-(2-fluoro-6-methoxyphenyl)-3-iodo-1H-pyrazolo[4,3-d]pyrimidine (from previous step) and [[β-(trimethylsilyl)ethoxy)methyl] chloride (2.00 mL, 11.3 mmol) in tetrahydrofuran (25 mL). After stirring at r.t. for 1 h, the reaction mixture was quenched by the addition of water and the product was extracted with ethyl acetate. The organic phase was washed with brine and dried over sodium sulfate. The solvents were evaporated under reduced pressure and the crude product was purified by Biotage Isolera™ (900 mg, 20% over 3 steps). LCMS calculated for  $C_{18}H_{23}FIN_4O_2Si$  (M+H)<sup>+</sup> m/z=501.1; found 501.0.

Step 6. 5-(2-Fluoro-6-methoxyphenyl)-3-phenyl-1H-pyrazolo[4,3-d]pyrimidine

[0500]

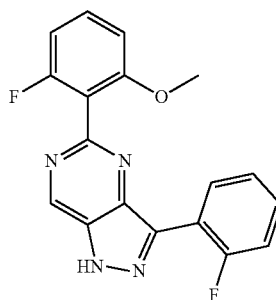


[0501] 5-(2-Fluoro-6-methoxyphenyl)-3-iodo-1-{{2-(trimethylsilyl)ethoxy)methyl}}-1H-pyrazolo[4,3-d]pyrimidine (15 mg, 0.030 mmol), phenylboronic acid (5.5 mg, 0.045 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (Pd XPhos G2) (2.4 mg, 0.0030 mmol), potassium phosphate (13 mg, 0.062 mmol) and a magnet bar were placed in a vial with septum which was then evacuated and backfilled with nitrogen three times. 1,4-Dioxane (1.5 mL) and degassed water (0.2 mL) were added and the reaction mixture was stirred at 80° C. for 1 h. Then 1M solution of HCl in water (1 mL) and 4M solution of HCl in dioxane (1 mL) were added, and reaction was stirred at 80° C. for 1 h. Methanol (1 mL) was added and reaction was further stirred at 80° C. for 30 min. The reaction mixture was then diluted with acetonitrile and was purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS calculated for  $C_{18}H_{14}FN_4O$  (M+H)<sup>+</sup>: m/z=321.1; Found: 321.2.

Example 13

5-(2-Fluoro-6-methoxyphenyl)-3-(2-fluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0502]

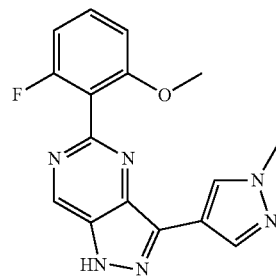


[0503] This compound was prepared according to the procedures described in Example 12, using 2-fluorophenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{18}H_{13}F_2N_4O$  (M+H)<sup>+</sup>: m/z=339.1; Found: 339.1.

Example 14

5-(2-Fluoro-6-methoxyphenyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0504]

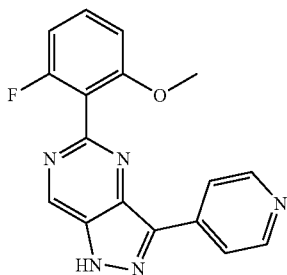


**[0505]** This compound was prepared according to the procedures described in Example 12, using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{16}H_{14}FN_6O$  ( $M+H$ )<sup>+</sup>:  $m/z=325.1$ ; Found: 325.2.

#### Example 15

5-(2-Fluoro-6-methoxyphenyl)-3-(pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine

**[0506]**

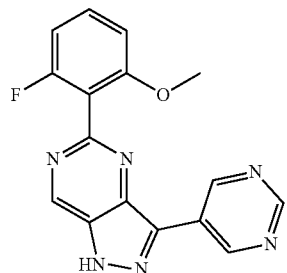


**[0507]** This compound was prepared according to the procedures described in Example 12, using pyridin-4-ylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{17}H_{13}FN_5O$  ( $M+H$ )<sup>+</sup>:  $m/z=322.1$ ; Found: 322.2.

#### Example 16

5-(2-Fluoro-6-methoxyphenyl)-3-(pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidine

**[0508]**

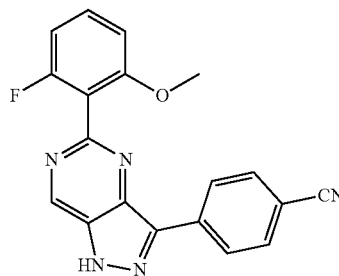


**[0509]** This compound was prepared according to the procedures described in Example 12, using pyrimidin-5-ylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{16}H_{12}FN_6O$  ( $M+H$ )<sup>+</sup>:  $m/z=323.1$ ; Found: 323.2.

#### Example 17

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzonitrile

**[0510]**

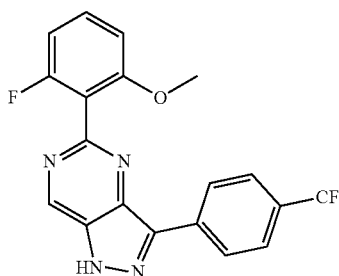


**[0511]** This compound was prepared according to the procedures described in Example 12, using 4-cyanophenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{19}H_{13}FN_5O$  ( $M+H$ )<sup>+</sup>:  $m/z=346.1$ ; Found: 346.2.

#### Example 18

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

**[0512]**

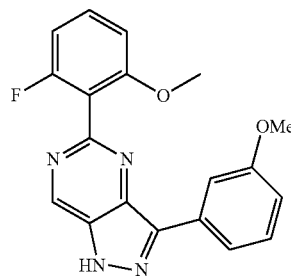


**[0513]** This compound was prepared according to the procedures described in Example 12, using 4-(trifluoromethyl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{19}H_{13}F_4N_4O$  ( $M+H$ )<sup>+</sup>:  $m/z=389.1$ ; Found: 389.2.

#### Example 19

5-(2-Fluoro-6-methoxyphenyl)-3-(3-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine

**[0514]**

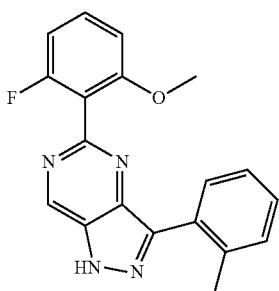


[0515] This compound was prepared according to the procedures described in Example 12, using 3-methoxyphenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{19}H_{16}FN_4O_2$  ( $M+H$ )<sup>+</sup>:  $m/z=351.1$ ; Found: 351.1.

#### Example 20

5-(2-Fluoro-6-methoxyphenyl)-3-o-tolyl-1H-pyrazolo[4,3-d]pyrimidine

[0516]

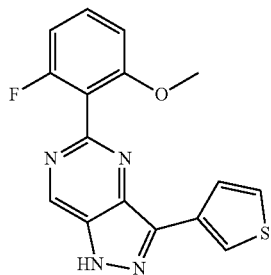


[0517] This compound was prepared according to the procedures described in Example 12, using o-tolylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{19}H_{16}FN_4O$  ( $M+H$ )<sup>+</sup>:  $m/z=335.1$ ; Found: 335.1.

#### Example 21

5-(2-Fluoro-6-methoxyphenyl)-3-(thiophen-3-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0518]

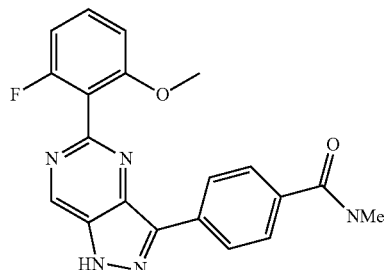


[0519] This compound was prepared according to the procedures described in Example 12, using thiophen-3-ylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{16}H_{12}FN_4OS$  ( $M+H$ )<sup>+</sup>:  $m/z=327.1$ ; Found: 327.1.

#### Example 22

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N,N-dimethylbenzamide

[0520]

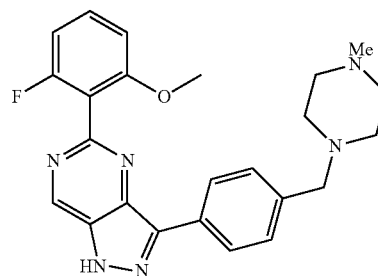


[0521] This compound was prepared according to the procedures described in Example 12, using N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{21}H_{19}FN_5O_2$  ( $M+H$ )<sup>+</sup>:  $m/z=392.2$ ; Found: 392.3.

#### Example 23

5-(2-Fluoro-6-methoxyphenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0522]

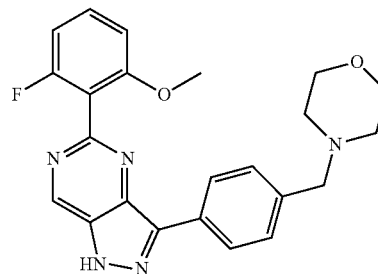


[0523] This compound was prepared according to the procedures described in Example 12, using 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{24}H_{26}FN_6O$  ( $M+H$ )<sup>+</sup>:  $m/z=433.2$ ; Found: 433.3.

#### Example 24

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzylmorpholine

[0524]



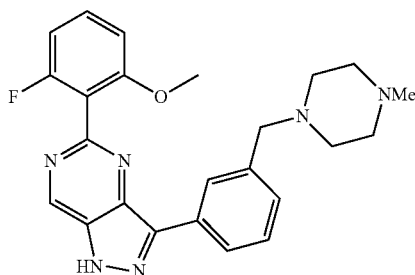


[0525] This compound was prepared according to the procedures described in Example 12, using 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{23}H_{23}FN_5O_2$  (M+H)<sup>+</sup>: m/z=420.2; Found: 420.3.

#### Example 25

5-(2-Fluoro-6-methoxyphenyl)-3-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0526]

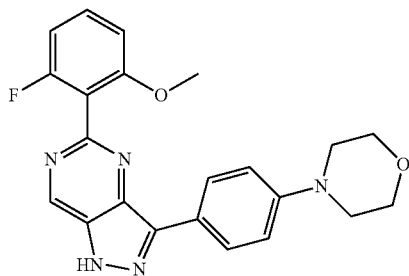


[0527] This compound was prepared according to the procedures described in Example 12, using 1-methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{24}H_{26}FN_6O$  (M+H)<sup>+</sup>: m/z=433.2; Found: 433.3.

#### Example 26

4-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)morpholine

[0528]

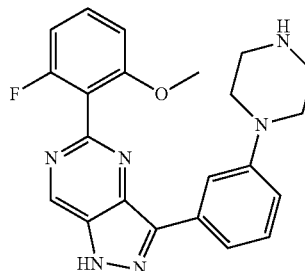


[0529] This compound was prepared according to the procedures described in Example 12, using 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{22}H_{21}FN_5O_2$  (M+H)<sup>+</sup>: m/z=406.2; Found: 406.3.

#### Example 27

5-(2-Fluoro-6-methoxyphenyl)-3-(3-(piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0530]

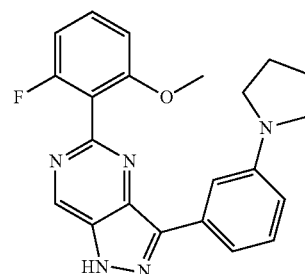


[0531] This compound was prepared according to the procedures described in Example 12, using tert-butyl 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{22}H_{22}FN_6O$  (M+H)<sup>+</sup>: m/z=405.2; Found: 405.2.

#### Example 28

5-(2-fluoro-6-methoxyphenyl)-3-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0532]

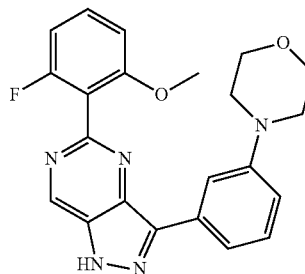


[0533] This compound was prepared according to the procedures described in Example 12, using 3-(pyrrolidin-1-yl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{22}H_{21}FN_5O$  (M+H)<sup>+</sup>: m/z=390.2; Found: 390.2.

#### Example 29

4-(3-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)morpholine

[0534]

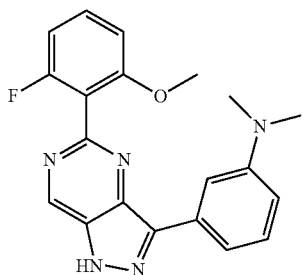


**[0535]** This compound was prepared according to the procedures described in Example 12, using 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{22}H_{21}FN_5O_2$  (M+H)<sup>+</sup>: m/z=406.2; Found: 406.2.

### Example 30

3-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N,N-dimethylaniline

**[0536]**

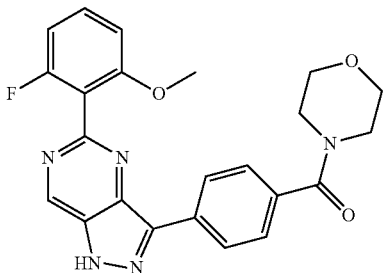


**[0537]** This compound was prepared according to the procedures described in Example 12, using 3-(dimethylamino)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{20}H_{19}FN_5O$  (M+H)<sup>+</sup>: m/z=364.2; Found: 364.2.

### Example 31

(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)(morpholino)methanone

**[0538]**

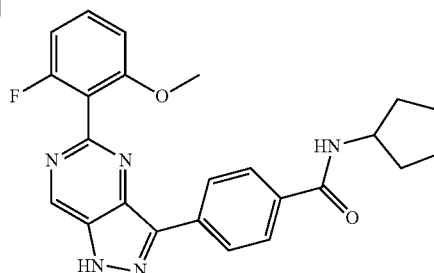


**[0539]** This compound was prepared according to the procedures described in Example 12, using 4-(morpholine-4-carbonyl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{23}H_{21}FN_5O_3$  (M+H)<sup>+</sup>: m/z=434.2; Found: 434.2.

### Example 32

N-Cyclopentyl-4-(5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzamide

**[0540]**

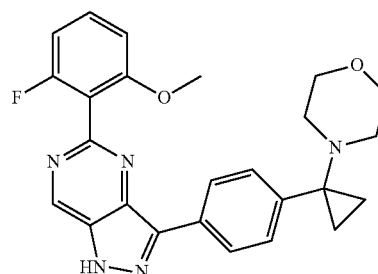


**[0541]** This compound was prepared according to the procedures described in Example 12, using 4-(cyclopentylcarbamoyl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{24}H_{23}FN_5O_2$  (M+H)<sup>+</sup>: m/z=432.2; Found: 432.3.

### Example 33

4-(1-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)cyclopropyl)morpholine

**[0542]**

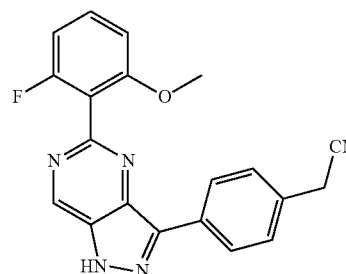


**[0543]** This compound was prepared according to the procedures described in Example 12, using 4-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)morpholine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{25}H_{25}FN_5O_2$  (M+H)<sup>+</sup>: m/z=446.2; Found: 446.3.

### Example 34

2-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)acetonitrile

**[0544]**

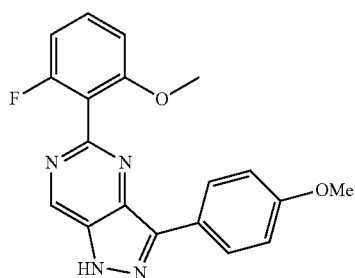


[0545] This compound was prepared according to the procedures described in Example 12, using 4-(cyanomethyl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{20}H_{15}FN_5O$  ( $M+H$ )<sup>+</sup>:  $m/z=360.1$ ; Found: 360.1.

#### Example 35

5-(2-Fluoro-6-methoxyphenyl)-3-(4-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0546]

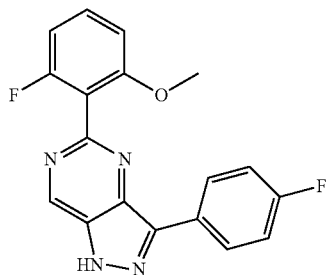


[0547] This compound was prepared according to the procedures described in Example 12, using 4-methoxyphenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{19}H_{16}FN_4O_2$  ( $M+H$ )<sup>+</sup>:  $m/z=351.1$ ; Found: 351.1.

#### Example 36

5-(2-Fluoro-6-methoxyphenyl)-3-(4-fluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0548]

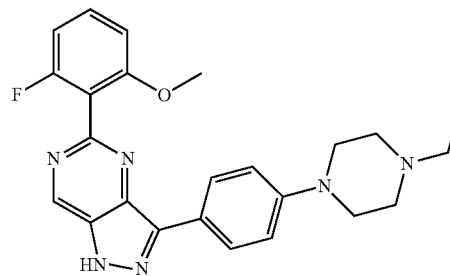


[0549] This compound was prepared according to the procedures described in Example 12, using 4-fluorophenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{18}H_{13}F_2N_4O$  ( $M+H$ )<sup>+</sup>:  $m/z=339.1$ ; Found: 339.2.

#### Example 37

3-(4-(4-Ethylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0550]

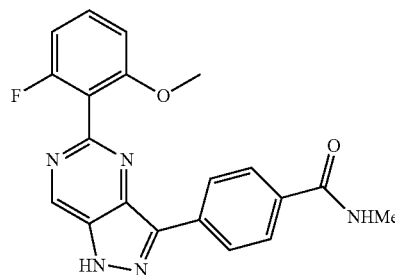


[0551] This compound was prepared according to the procedures described in Example 12, using 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{24}H_{26}FN_6O$  ( $M+H$ )<sup>+</sup>:  $m/z=433.2$ ; Found: 433.3.

#### Example 38

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N-methylbenzamide

[0552]

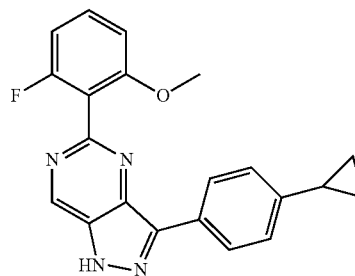


[0553] This compound was prepared according to the procedures described in Example 12, using 4-(methylcarbamoyl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{20}H_{17}FN_5O_2$  ( $M+H$ )<sup>+</sup>:  $m/z=378.1$ ; Found: 378.

#### Example 39

3-(4-Cyclopropylphenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0554]

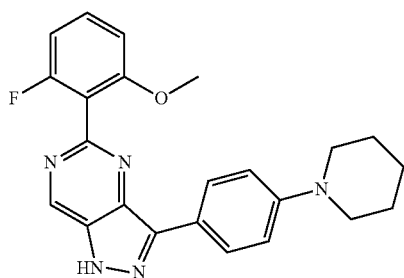


[0555] This compound was prepared according to the procedures described in Example 12, using 4-cyclopropylphenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{21}H_{18}FN_4O$  (M+H)<sup>+</sup>: m/z=361.2; Found: 361.2.

## Example 40

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0556]

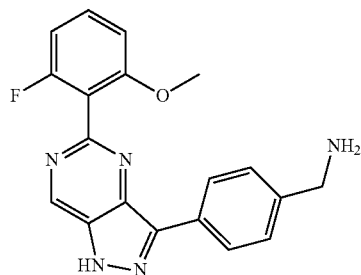


[0557] This compound was prepared according to the procedures described in Example 12, using 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{23}H_{23}FN_5O$  (M+H)<sup>+</sup>: m/z=404.2; Found: 404.2.

## Example 41

(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)methanamine

[0558]

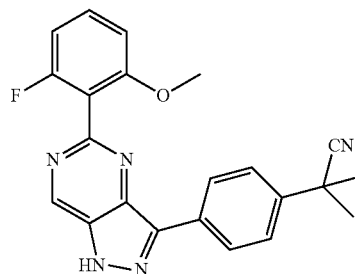


[0559] This compound was prepared according to the procedures described in Example 12, using 4-((tert-butoxycarbonylamino)methyl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{19}H_{17}FN_5O$  (M+H)<sup>+</sup>: m/z=350.1; Found: 350.0.

## Example 42

2-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)-2-methylpropanenitrile

[0560]

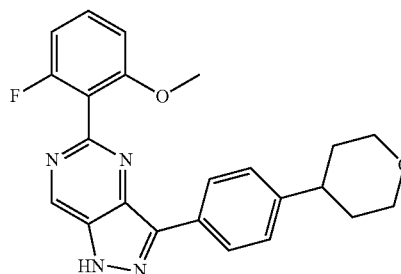


[0561] This compound was prepared according to the procedures described in Example 12, using 4-(2-cyanopropan-2-yl)phenylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{22}H_{19}FN_5O$  (M+H)<sup>+</sup>: m/z=388.2; Found: 388.2.

## Example 43

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0562]

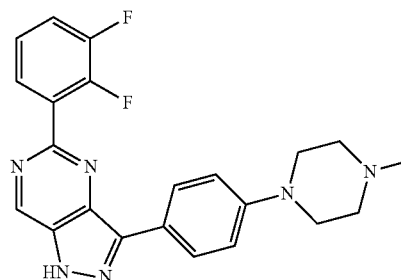


[0563] This compound was prepared according to the procedures described in Example 12, using 4,4,5,5-tetramethyl-2-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,3,2-dioxaborolane, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{23}H_{22}FN_4O_2$  (M+H)<sup>+</sup>: m/z=405.2; Found: 405.2.

## Example 44

5-(2,3-Difluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0564]

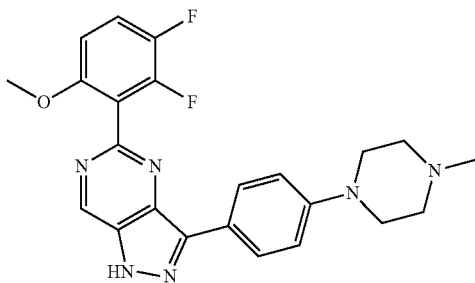


**[0565]** This compound was prepared according to the procedures described in Example 1, using (2,3-difluorophenyl)boronic acid, instead of (2-fluorophenyl)boronic acid as starting material. LC-MS calculated for  $C_{22}H_{21}F_2N_6$  (M+H)<sup>+</sup>: m/z=407.2; Found 407.2.

#### Example 45

5-(2,3-Difluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

**[0566]**

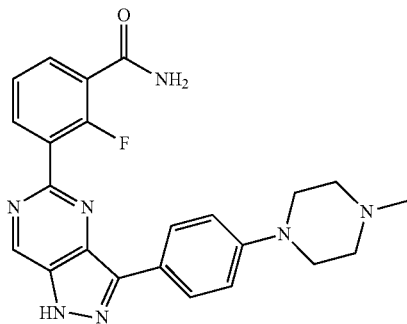


**[0567]** This compound was prepared according to the procedures described in Example 1, using (2,3-difluoro-6-methoxyphenyl)boronic, instead of (2-fluorophenyl)boronic acid as starting material. LC-MS calculated for  $C_{23}H_{23}F_2N_6O$  (M+H)<sup>+</sup>: m/z=437.2; Found 437.2.

#### Example 46

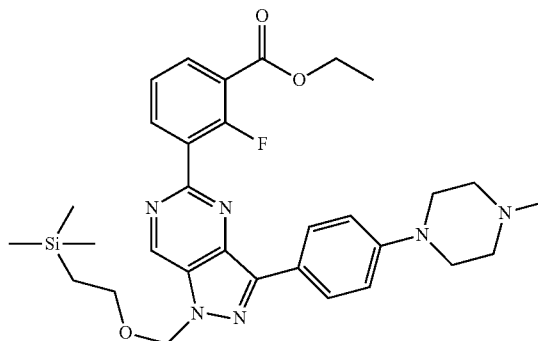
2-Fluoro-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzamide

**[0568]**



Step 1. Ethyl 2-fluoro-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzoate

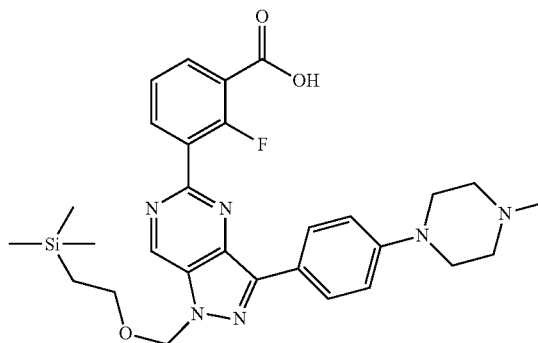
**[0569]**



**[0570]** To a solution of 5-chloro-3-[4-(4-methylpiperazin-1-yl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-d]pyrimidine (Example 1 Step 3, 0.100 g, 0.218 mmol) and (3-(ethoxycarbonyl)-2-fluorophenyl)boronic acid (0.092 g, 0.436 mmol) in 1,4-dioxane (2.90 ml) and water (0.726 ml) was added chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.017 g, 0.022 mmol) and potassium phosphate tribasic (0.092 g, 0.436 mmol). The reaction mixture was degassed and stirred at 90° C. for 2 hours. After cooling to r.t., the reaction was filtered and concentrated to dryness under reduced pressure. The residue was purified by Biotage Isolera™ using 0-10% DCM in methanol to afford the desired product as yellowish oil. LC-MS calculated for  $C_{31}H_{40}FN_6O_3Si$  (M+H)<sup>+</sup>: m/z=591.2; Found 591.2.

Step 2. 2-Fluoro-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzoic acid

**[0571]**

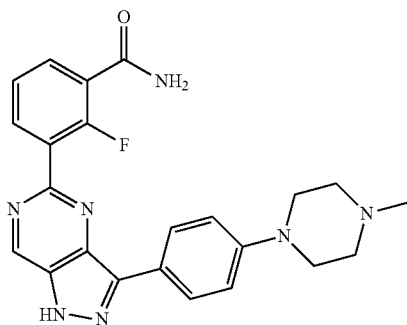


**[0572]** To a solution of the above intermediate in methanol (0.726 ml) was added potassium hydroxide (0.122 g, 2.178 mmol), and the reaction mixture was stirred at r.t. for 1 hour. After this time the reaction mixture was concentrated to dryness, diluted with ethyl acetate and washed with 1N water solution of HCl (10 mL) and brine. The organic layer was dried over  $MgSO_4$ , filtered and concentrated to dryness

to afford a crude desired product which was used in the next step without further purification. LC-MS calculated for  $C_{29}H_{36}FN_6O_3Si$  (M+H)<sup>+</sup>: m/z=563.2; Found 563.2.

Step 3. 2-Fluoro-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzamide

[0573]

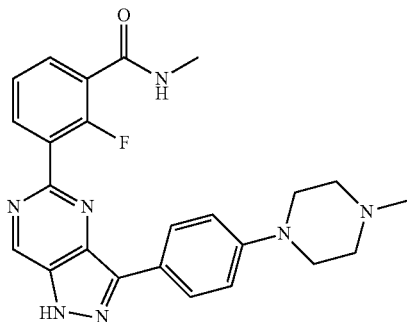


[0574] To a solution of 2-fluoro-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzoic acid (30 mg, 0.053 mmol) in DMF (1 mL) were added 2.0M solution of ammonia in ethanol (267  $\mu$ L, 0.533 mmol) and N,N-diisopropylethylamine (37.2  $\mu$ L, 0.213 mmol), followed by the addition of HATU (81 mg, 0.213 mmol). The reaction mixture was then stirred at r.t. for 2 hours. After this time 4M HCl solution in dioxane (1.3 mL, 5.33 mmol) and 1N HCl solution in water (1.1 mL, 1.066 mmol) were added and the mixture was stirred for another 1 hour at 80° C. It was then cooled to r.t., diluted with methanol, filtered and purified by prep-HPLC. (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LC-MS calculated for  $C_{23}H_{23}FN_7O$  (M+H)<sup>+</sup>: m/z=432.2; Found 432.2.

Example 47

2-Fluoro-N-methyl-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzamide

[0575]

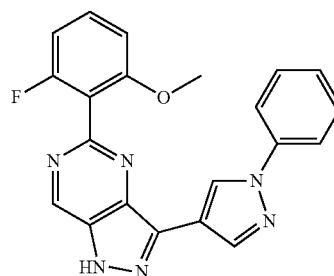


[0576] This compound was prepared according to the procedures described in Example 46, using 2.0M solution of methylamine in THF instead of 2.0M solution of ammonia in ethanol as starting material. LC-MS calculated for  $C_{24}H_{23}FN_7O$  (M+H)<sup>+</sup>: m/z=446.2; Found 446.2.

Example 48

5-(2-Fluoro-6-methoxyphenyl)-3-(1-phenyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0577]

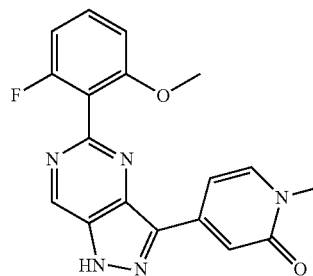


[0578] This compound was prepared according to the procedures described in Example 12, using 1-phenyl-1H-pyrazol-4-ylboronic acid, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{21}H_{16}FN_6O$  (M+H)<sup>+</sup>: m/z=387.1; Found: 387.2.

Example 49

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1-methylpyridin-2(1H)-one

[0579]

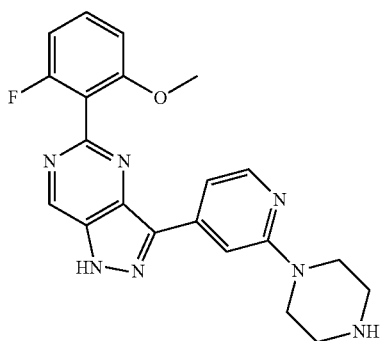


[0580] This compound was prepared according to the procedures described in Example 12, using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{18}H_{15}FN_5O_2$  (M+H)<sup>+</sup>: m/z=352.1; Found: 352.2.

## Example 50

5-(2-Fluoro-6-methoxyphenyl)-3-(2-(piperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0581]

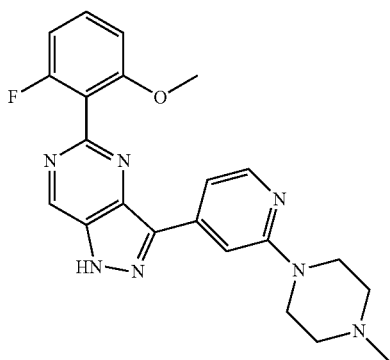


[0582] This compound was prepared according to the procedures described in Example 12, using 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{21}H_{21}FN_7O$  ( $M+H$ )<sup>+</sup>:  $m/z=406.2$ ; Found: 406.2.

## Example 51

5-(2-Fluoro-6-methoxyphenyl)-3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0583]

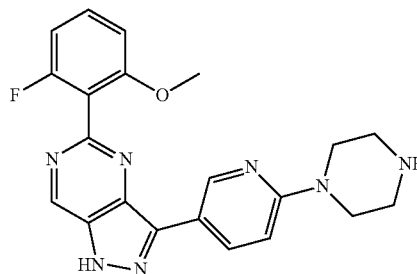


[0584] This compound was prepared according to the procedures described in Example 12, using 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{22}H_{23}FN_7O$  ( $M+H$ )<sup>+</sup>:  $m/z=420.2$ ; Found: 420.2.

## Example 52

5-(2-Fluoro-6-methoxyphenyl)-3-(6-(piperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0585]

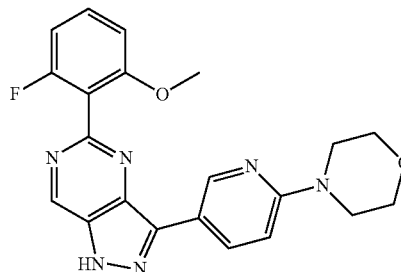


[0586] This compound was prepared according to the procedures described in Example 12, using tert-butyl 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{21}H_{21}FN_7O$  ( $M+H$ )<sup>+</sup>:  $m/z=406.2$ ; Found: 406.2.

## Example 53

4-(5-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)morpholine

[0587]

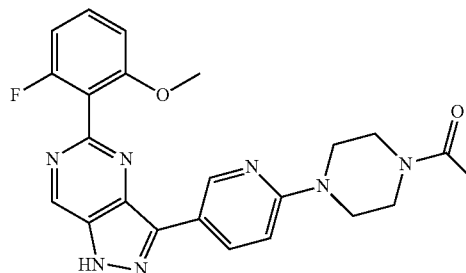


[0588] This compound was prepared according to the procedures described in Example 12, using 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{21}H_{20}FN_6O_2$  ( $M+H$ )<sup>+</sup>:  $m/z=407.2$ ; Found: 407.2.

## Example 54

1-(4-(5-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)piperazin-1-yl)ethan-1-one

[0589]

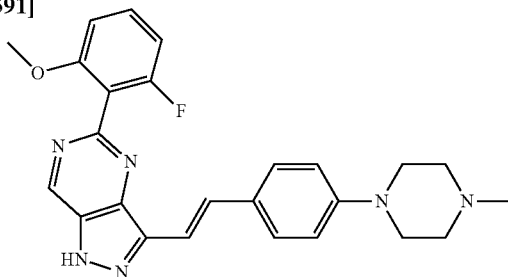


**[0590]** This compound was prepared according to the procedures described in Example 12, using 1-(4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazin-1-yl)ethan-1-one, instead of phenylboronic acid as starting material. LCMS calculated for  $C_{23}H_{23}FN_7O_2$  ( $M+H$ )<sup>+</sup>:  $m/z=448.2$ ; Found: 448.2.

#### Example 55

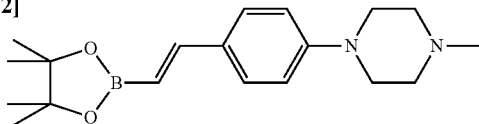
(E)-5-(2-Fluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)styryl)-1H-pyrazolo[4,3-d]pyrimidine

**[0591]**



Step 1. (E)-1-Methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine

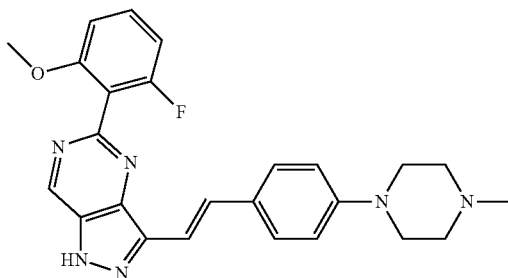
**[0592]**



**[0593]** A mixture of 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (135 mg, 0.875 mmol), 1-(4-bromophenyl)-4-methylpiperazine (186 mg, 0.729 mmol), bis(tri-*t*-butylphosphine)palladium (0) (18.6 mg, 0.036 mmol) and triethylamine (0.203 mL, 1.46 mmol) in toluene (3.0 mL) was stirred at 80° C. under nitrogen atmosphere for 4 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude was purified by Biotage Isolera™ (eluting with a gradient 0-50% methanol in DCM) to give the desired product as yellow solid (109 mg, 46%). LCMS calculated for  $C_{19}H_{30}BN_2O_2$  ( $M+H$ )<sup>+</sup>:  $m/z=329.2$ ; Found: 329.2.

Step 2. (E)-5-(2-Fluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)styryl)-1H-pyrazolo[4,3-d]pyrimidine

**[0594]**

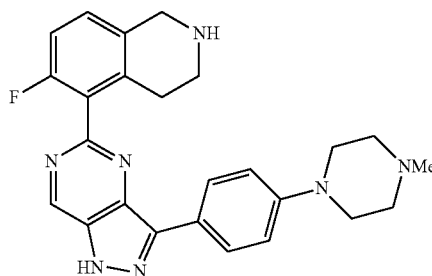


**[0595]** A mixture of 5-(2-fluoro-6-methoxyphenyl)-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (Example 12, Step 5, 56.0 mg, 0.112 mmol), (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine (55.1 mg, 0.168 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium (II) complex with dichloromethane (1:1) (4.09 mg, 0.0056 mmol) and potassium phosphate (47.5 mg, 0.224 mmol) in 1,4-dioxane (2.0 mL) and water (0.4 mL) was stirred at 80° C. under nitrogen atmosphere for 18 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude mixture was then dissolved in DCM (2.0 mL) and TFA (2.0 mL) was added to the mixture at room temperature. After stirring for 2 h, the mixture was concentrated in vacuo. Then, the crude mixture was dissolved in MeOH (3.5 mL) and 10% aqueous  $NH_4OH$  solution (1.5 mL) was added. After stirring for 30 min, the reaction mixture was purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water (pH=2), at flow rate of 60 mL/min) to give the desired product as yellow solid. LCMS calculated for  $C_{25}H_{26}FN_6O$  ( $M+H$ )<sup>+</sup>:  $m/z=445.2$ ; Found: 445.3.  $^1H$  NMR (600 MHz,  $DMSO-d_6$ )  $\delta$  9.89 (br, 1H), 9.40 (s, 1H), 7.86 (d,  $J=16.5$  Hz, 1H), 7.65 (d,  $J=8.8$  Hz, 2H), 7.50 (m, 1H), 7.38 (d,  $J=16.5$  Hz, 1H), 7.02 (m, 3H), 6.96 (t,  $J=8.6$  Hz, 1H), 3.93 (m, 2H), 3.73 (s, 3H), 3.45 (m, 2H), 3.14 (m, 2H), 3.02 (m, 2H), 2.86 (s, 3H) ppm.

#### Example 56

6-Fluoro-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

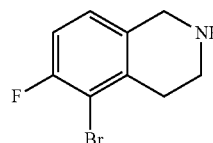
**[0596]**



#### Step 1.

5-Bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline

**[0597]**



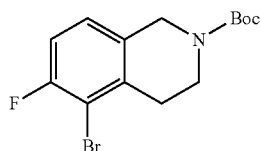
**[0598]** To a solution of 5-bromo-6-fluoroisoquinoline (1.002 g, 4.433 mmol) in acetic acid (20.0 mL) at room temperature was added sodium tetrahydroborate (592.0 mg, 15.65 mmol) portionwise. The mixture was stirred at room



temperature for 16 h, and then concentrated. The residue was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with 2 M  $\text{Na}_2\text{CO}_3$  (aq). The separated organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give a yellow oil, which was used directly in the next step without further purification. LCMS calculated for  $\text{C}_9\text{H}_{10}\text{BrFN}$  ( $\text{M}+\text{H}$ ) $^+$   $m/z=230.0$ ; found 230.1.

Step 2. tert-Butyl 5-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate

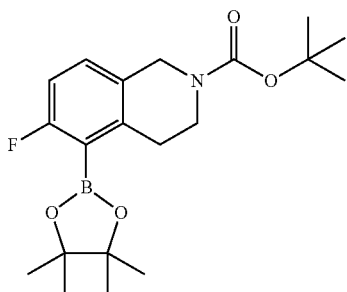
[0599]



[0600] To a solution of 5-bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline (1.020 g, 4.433 mmol) in  $\text{CH}_2\text{Cl}_2$  (12.0 mL) was added di-tert-butyl dicarbonate (1.617 g, 7.409 mmol). The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (1.119 g, 76% over two steps). LCMS calculated for  $\text{C}_{14}\text{H}_{17}\text{BrFNNaO}_2$  ( $\text{M}+\text{Na}$ ) $^+$   $m/z=352.0$ ; found 352.0.

Step 3. tert-Butyl 6-fluoro-5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[0601]

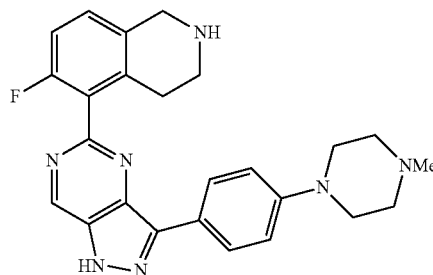


[0602] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.119 g, 3.389 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (1.358 g, 5.348 mmol), potassium acetate (1.101 g, 11.22 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (298.6 mg, 0.366 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (15.0 mL) was added via syringe. The mixture was heated at 100° C. for 16 h. After cooling to room temperature, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and filtered. The filtrate was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as

a pale yellow oil (1001 mg, 78%). LCMS calculated for  $\text{C}_{20}\text{H}_{29}\text{BFNNaO}_4$  ( $\text{M}+\text{Na}$ ) $^+$   $m/z=400.2$ ; found 400.2.

Step 4. 6-Fluoro-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0603]

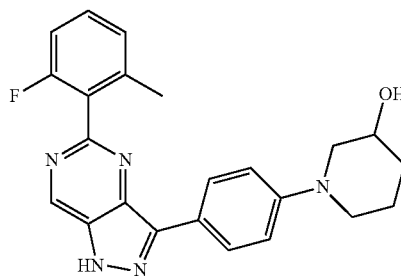


[0604] To a screw-cap vial equipped with a magnetic stir bar was added 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (Example 12, Step 5, 50.9 mg, 0.111 mmol), XPhos Pd G2 (9.5 mg, 0.012 mmol) and  $\text{K}_3\text{PO}_4$  (78.2 mg, 0.368 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (44.9 mg, 0.119 mmol) in 1,4-dioxane (2.0 mL) was added via syringe, followed by degassed water (150.0  $\mu\text{L}$ ). The mixture was heated at 80° C. for 1 h. After cooling to room temperature, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and filtered. The filtrate was concentrated. The residue was dissolved in methanol (3.00 mL) and treated with 4.0 M HCl in dioxane (2.00 mL, 8.00 mmol). The mixture was stirred at 65° C. for 2 h. After cooling to room temperature, the mixture was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product as a yellow solid (22.4 mg). LCMS calculated for  $\text{C}_{25}\text{H}_{27}\text{FN}_7$  ( $\text{M}+\text{H}$ ) $^+$   $m/z=444.2$ ; Found: 444.2.

Example 57

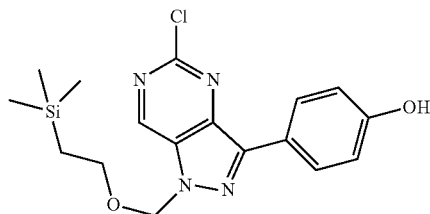
1-(4-(5-(2-Fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperidin-3-ol

[0605]



Step 1. 4-(5-Chloro-1-(2-(trimethylsilyl)ethoxy)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenol

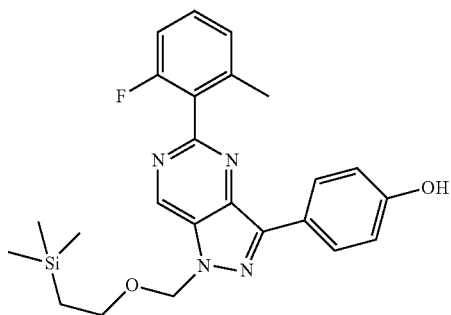
[0606]



[0607] To a solution of 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (4.0 g, 9.74 mmol, Example 1, Step 2) in dioxane (39.0 ml) and water (9.74 ml) was added potassium phosphate (4.13 g, 19.5 mmol) and (4-hydroxyphenyl)boronic acid (1.34 g, 9.74 mmol) followed by addition of  $\text{PdCl}_2(\text{dppf})$  (0.795 g, 0.974 mmol).  $\text{N}_2$  was bubbled through the mixture for 5 mins, and then it was stirred at  $90^\circ\text{C}$ . for 2 hours. After this time, the mixture was cooled to r.t. and then concentrated to dryness. The residue was purified by silica gel chromatography using 0-10% methanol in DCM to afford desired product as brownish oil (590 mg, 16.1%). LC-MS calculated for  $\text{C}_{17}\text{H}_{22}\text{ClN}_4\text{O}_2\text{Si}$  ( $\text{M}+\text{H}^+$ ):  $m/z=377.2$ ; found 377.1.

Step 2. 4-(5-(2-Fluoro-6-methylphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenol

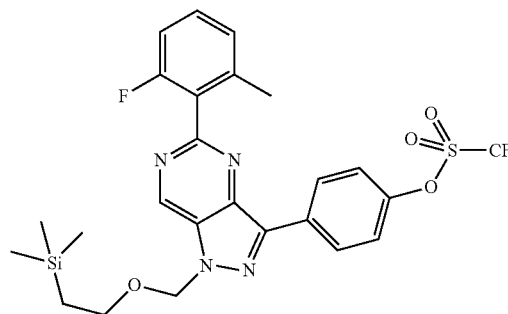
[0608]



[0609] To a solution of 4-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenol (660 mg, 1.75 mmol) in dioxane (14 ml) and water (3.5 ml) was added potassium phosphate (742 mg, 3.50 mmol) and (2-fluoro-6-methylphenyl)boronic acid (404 mg, 2.63 mmol) followed by chloro(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (138 mg, 0.175 mmol).  $\text{N}_2$  was bubbled through the mixture for 5 mins and then it was stirred at  $80^\circ\text{C}$ . for 2 hours. After this time the mixture was cooled to r.t. and then concentrated to dryness. The residue was purified by silica gel chromatography using 0-10% methanol in DCM to afford desired product as brownish oil (390 mg, 49.4%). LC-MS calculated for  $\text{C}_{24}\text{H}_{28}\text{FN}_4\text{Si}$  ( $\text{M}+\text{H}^+$ ):  $m/z=451.2$ ; found 451.2.

Step 3. 4-(5-(2-Fluoro-6-methylphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl trifluoromethanesulfonate

[0610]



[0611] To a solution of 4-(5-(2-fluoro-6-methylphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenol (990 mg, 2.2 mmol) in DMF (22 ml) was added sodium hydride (132 mg, 3.30 mmol, 60% in mineral oil). After stirring at r.t. for 10 min, *N*-phenyltrifluoromethanesulfonimide (942 mg, 2.64 mmol) was added. The resulting solution was stirred at r.t. for 30 mins, and then quenched by  $\text{NH}_4\text{Cl}$  aq. solution. The product was then extracted with ethyl acetate. The organic layer was washed with water and brine, and then dried over  $\text{MgSO}_4$ , filtered and concentrated to dryness. The residue was purified by silica gel chromatography using 0-100% ethyl acetate in hexanes to afford desired product as brownish oil (460 mg, 35.9%). LC-MS calculated for  $\text{C}_{25}\text{H}_{27}\text{F}_4\text{N}_4\text{O}_4\text{SSi}$  ( $\text{M}+\text{H}^+$ ):  $m/z=583.1$ ; found 583.1

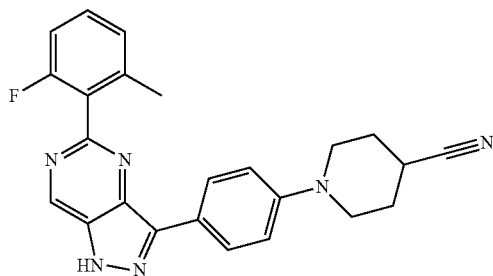
Step 4. 1-(4-(5-(2-Fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperidin-3-ol

[0612] To a solution of 4-(5-(2-fluoro-6-methylphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl trifluoromethanesulfonate (30 mg, 0.051 mmol) in dioxane (8 mL) was added cesium carbonate (33.6 mg, 0.103 mmol) and piperidin-3-ol (26.0 mg, 0.257 mmol). The mixture was degassed and chloro(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (4.00 mg, 5.15  $\mu\text{mol}$ ) was added. The resulting mixture was stirred at  $90^\circ\text{C}$ . for 2 hours. After this time, the mixture was filtered, and 4.0 M  $\text{HCl}$  in dioxane (1 mL, 4 mmol) and 1 mL of water were added. The reaction mixture was stirred for another 1 hour at  $80^\circ\text{C}$ . After this time, 1 mL of methanol was added and the reaction mixture was stirred for another 30 min at  $80^\circ\text{C}$ . The mixture was then diluted with acetonitrile, filtered and purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LC-MS calculated for  $\text{C}_{23}\text{H}_{23}\text{FN}_5\text{O}$  ( $\text{M}+\text{H}^+$ ):  $m/z=404.2$ ; found 404.2.

## Example 58

1-(4-(5-(2-Fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperidine-4-carbonitrile

[0613]

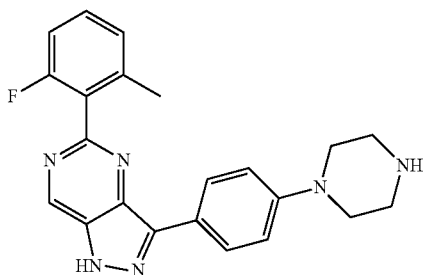


[0614] This compound was prepared according to the procedure described in Example 57, using piperidine-4-carbonitrile instead of piperidin-3-ol as starting material. LC-MS calculated for  $C_{24}H_{22}FN_6$  (M+H)<sup>+</sup>: m/z=413.2; Found 413.2.

## Example 59

5-(2-Fluoro-6-methylphenyl)-3-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0615]

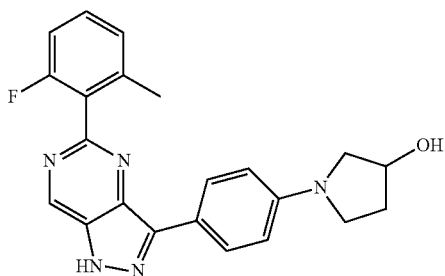


[0616] This compound was prepared according to the procedure described in Example 57, using piperazine instead of piperidin-3-ol as starting material. LC-MS calculated for  $C_{22}H_{22}FN_6$  (M+H)<sup>+</sup>: m/z=389.2; Found 389.2.

## Example 60

1-(4-(5-(2-Fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)pyrrolidin-3-ol

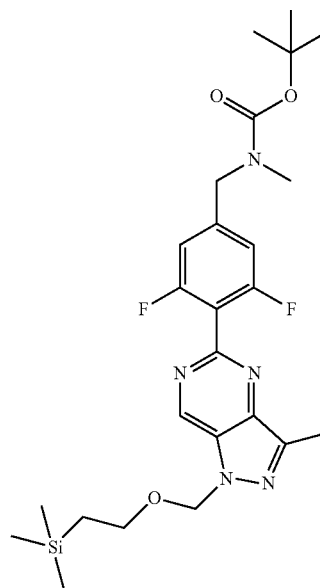
[0617]



[0618] This compound was prepared according to the procedure described in Example 57, using pyrrolidin-3-ol instead of piperidin-3-ol as starting material. LC-MS calculated for  $C_{22}H_{21}FN_5O$  (M+H)<sup>+</sup>: m/z=390.2; Found 390.2.

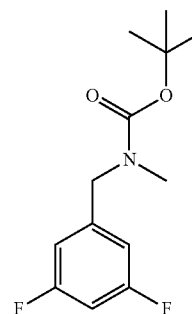
Intermediate 1. tert-Butyl 3,5-difluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzyl(methyl)carbamate

[0619]



Step 1. tert-Butyl 3,5-difluorobenzyl(methyl)carbamate

[0620]

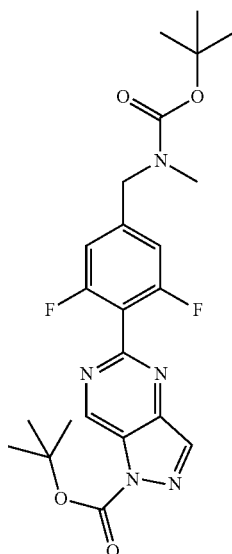


[0621] To a solution of 3,5-difluorobenzaldehyde (15.0 g, 106 mmol) in MeOH (528 ml) was added methylamine (79.0 ml, 158 mmol, 2M in THF), and the reaction mixture was stirred at r.t. for 1 hour. Sodium borohydride (7.99 g, 211 mmol) was added and the reaction was stirred until bubbling has stopped. The mixture was concentrated to dryness, and then dissolved in 300 mL of DCM. Sodium bicarbonate aq. solution was added and the reaction mixture was stirred at r.t. for another 1 hour. The organic layer was dried over  $MgSO_4$ , filtered and concentrated to dryness. The residue

was dissolved in DCM (528 ml), then DIPEA (18.4 ml, 106 mmol) and di-tert-butyl dicarbonate (24.5 ml, 106 mmol) were added. The resulting solution was stirred at r.t. for 1 hour. The solution was concentrated to dryness and the residue was purified by silica gel chromatography using 0-70% ethyl acetate in hexanes to afford desired product as colorless oil (15.1g, 55.4%). LC-MS calculated for  $C_9H_{10}F_2NO_2$  ( $M+2H-tBu$ )<sup>+</sup>:  $m/z=202.1$ ; Found 202.2.

Step 2. tert-Butyl 5-(4-((tert-butoxycarbonyl(methyl)amino)methyl)-2,6-difluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

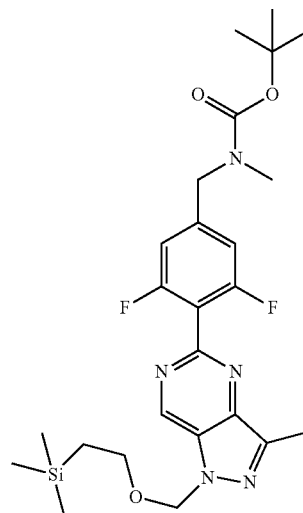
[0622]



[0623] To a solution of tert-butyl (3,5-difluorobenzyl)(methyl)carbamate (6.67 g, 25.9 mmol) in THF (120 ml) was added n-butyllithium (13.8 ml, 34.6 mmol) dropwise at  $-78^\circ\text{C}$ . and the reaction was stirred at  $-78^\circ\text{C}$ . for 1 hour. After this time 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.04 g, 43.2 mmol) was added and it was allowed to warm up to r.t. over 1 hour. The reaction mixture was quenched with water and the desired product was extracted with ethyl acetate. The organic layer was washed with brine, dried over  $MgSO_4$ , filtered and then concentrated to dryness. The residue was dissolved in dioxane (40 ml) and water (10.00 ml). To the resulting solution was added tert-butyl 5-chloro-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (2.2 g, 8.64 mmol) and potassium phosphate, tribasic (3.01 g, 17.3 mmol). The reaction was degassed and chloro(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II) (0.680 g, 0.864 mmol) was added. The solution was then stirred at  $60^\circ\text{C}$ . for 1 hour. After cooling to r.t. solvents were evaporated in vacuo and the residue was purified by silica gel chromatography using 0-10% methanol in DCM to afford desired product as yellowish oil (1.70 g, 41.4%). LC-MS calculated for  $C_{23}H_{28}F_2N_5O_4$  ( $M+H$ )<sup>+</sup>:  $m/z=476.2$ ; found 476.2.

Step 3. tert-Butyl 3,5-difluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzyl(methyl)carbamate

[0624]

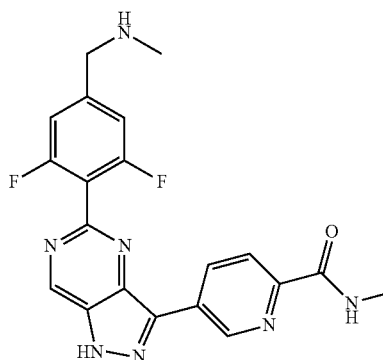


[0625] To a solution of tert-butyl 5-(4-((tert-butoxycarbonyl(methyl)amino)methyl)-2,6-difluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (1.60 g, 3.36 mmol) in dioxane (16.8 ml) and water (16.8 ml) was added potassium carbonate (2.3 g, 16.8 mmol) and the reaction was stirred at  $80^\circ\text{C}$ . for 2 hours. It was then cooled to r.t., diluted with DCM, washed with water, sodium bicarbonate aq. solution and brine. The organic layer was dried over  $MgSO_4$ , filtered and then concentrated to dryness. The residue was dissolved in acetonitrile (33.6 ml). To the resulting solution was added N-iodosuccinimide (643 mg, 2.86 mmol) and the reaction was stirred at  $50^\circ\text{C}$ . for 1 hour. After this time it was cooled to r.t. then DIPEA (588  $\mu\text{l}$ , 3.36 mmol) was added followed by addition of SEM-Cl (507  $\mu\text{l}$ , 2.86 mmol) dropwise. The resulting solution was stirred for 30 mins at r.t. then concentrated to dryness. The residue was purified by silica gel chromatography using 0-70% ethyl acetate in hexanes to afford Intermediate 1 as dark brownish solid (260 mg, 12.2%). LC-MS calculated for  $C_{24}H_{33}F_2IN_5O_3Si$  ( $M+H$ )<sup>+</sup>:  $m/z=632.2$ ; found 632.2.

Example 61

5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N-methylpicolinamide

[0626]

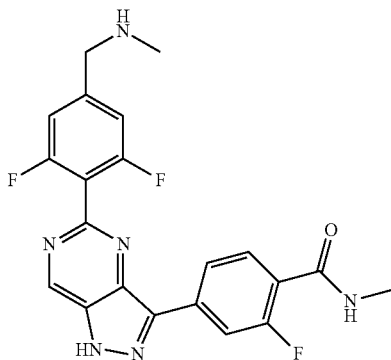


**[0627]** To a solution of Intermediate I (20 mg, 0.032 mmol) in dioxane (1 mL) and water (0.250 mL) was added potassium phosphate, tribasic (13 mg, 0.063 mmol) and N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) picolinamide (16 mg, 0.063 mmol). The mixture was degassed and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II) (4.98 mg, 6.33  $\mu$ mol) was added. The resulting mixture was stirred at 90° C. for 2 hours. The mixture was filtered, and 4.0 M HCl solution in dioxane (1 mL, 4.000 mmol) and 1 mL of water were added and the reaction mixture was stirred for another 1 hour at 80° C. 1 mL of methanol was added and the reaction mixture was stirred for another 30 mins at 80° C. The mixture was then diluted with acetonitrile, filtered and purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LC-MS calculated for  $C_{20}H_{18}F_2N_7O$  (M+H)<sup>+</sup>: m/z=410.2; found 410.2.

#### Example 62

4-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-fluoro-N-methylbenzamide

**[0628]**

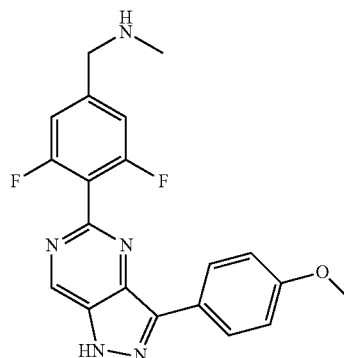


**[0629]** This compound was prepared according to the procedure described in Example 61, using 2-fluoro-N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{21}H_{18}F_3N_6O$  (M+H)<sup>+</sup>: m/z=427.2; Found 427.2.

#### Example 63

1-(3,5-Difluoro-4-(3-(4-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

**[0630]**

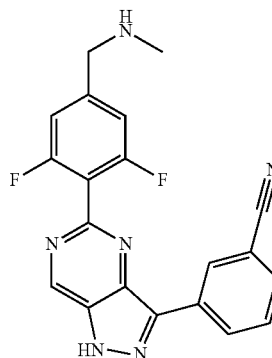


**[0631]** This compound was prepared according to the procedure described in Example 61, using 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{20}H_{18}F_2N_5O$  (M+H)<sup>+</sup>: m/z=382.2; Found 382.2.

#### Example 64

3-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzonitrile

**[0632]**

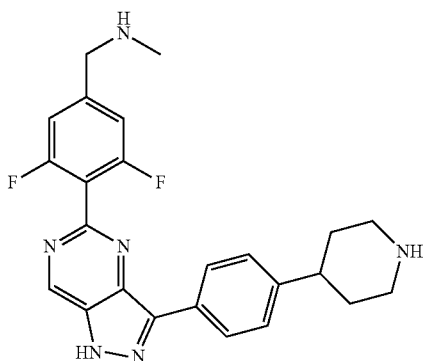


**[0633]** This compound was prepared according to the procedure described in Example 61, using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{20}H_{15}F_2N_6$  (M+H)<sup>+</sup>: m/z=377.2; Found 377.2.

## Example 65

1-(3,5-Difluoro-4-(3-(4-(piperidin-4-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0634]

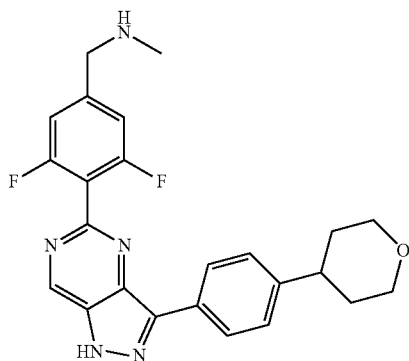


[0635] This compound was prepared according to the procedure described in Example 61, using tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{24}H_{25}F_2N_6$  (M+H)<sup>+</sup>: m/z=435.2; Found 435.2.

## Example 66

1-(3,5-Difluoro-4-(3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0636]

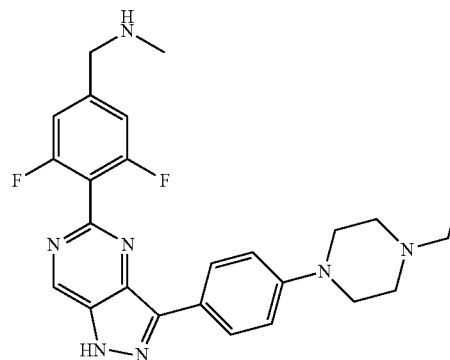


[0637] This compound was prepared according to the procedure described in Example 61, using 4,4,5,5-tetramethyl-2-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,3,2-dioxaborolane instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{24}H_{24}F_2N_5O$  (M+H)<sup>+</sup>: m/z=436.2; Found 436.2.

## Example 67

1-(4-(3-(4-(4-Ethylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-difluorophenyl)-N-methylmethanamine

[0638]

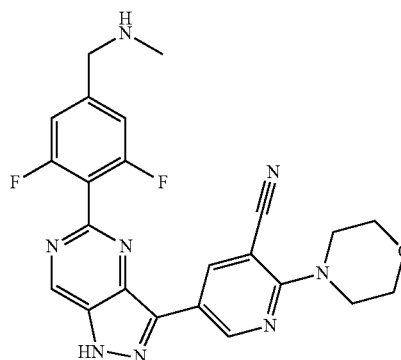


[0639] This compound was prepared according to the procedure described in Example 61, using 1-ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{25}H_{28}F_2N_7$  (M+H)<sup>+</sup>: m/z=464.2; Found 464.2. <sup>1</sup>H NMR (500 MHz, DMSO) δ 9.95 (s, 1H), 9.51 (s, 1H), 9.19 (s, 1H), 8.33 (d, J=8.8 Hz, 2H), 7.46 (d, J=8.2 Hz, 2H), 7.20 (d, J=9.0 Hz, 2H), 4.28 (s, 2H), 3.98 (d, J=12.4 Hz, 2H), 3.61 (d, J=9.8 Hz, 3H), 3.22 (q, J=7.3 Hz, 2H), 3.18-3.02 (m, 3H), 2.66 (s, 3H), 1.27 (t, J=7.2 Hz, 3H).

## Example 68

5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-morpholinonicotinonitrile

[0640]



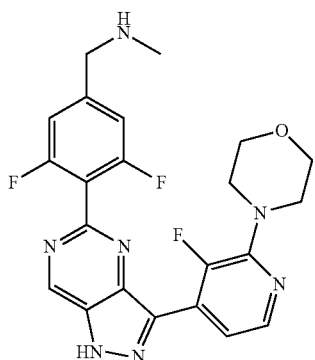
[0641] This compound was prepared according to the procedure described in Example 61, using 2-morpholino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material.

borolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{23}H_{21}F_2N_8O$  (M+H)<sup>+</sup>: m/z=463.2; Found 463.2.

### Example 69

1-(3,5-Difluoro-4-(3-(3-fluoro-2-morpholinopyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0642]

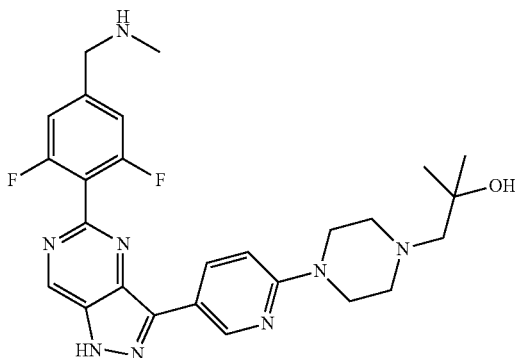


[0643] This compound was prepared according to the procedure described in Example 61, using 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine instead of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide as starting material. LC-MS calculated for  $C_{22}H_{21}F_3N_7O$  (M+H)<sup>+</sup>: m/z=456.2; Found 456.2.

### Example 70

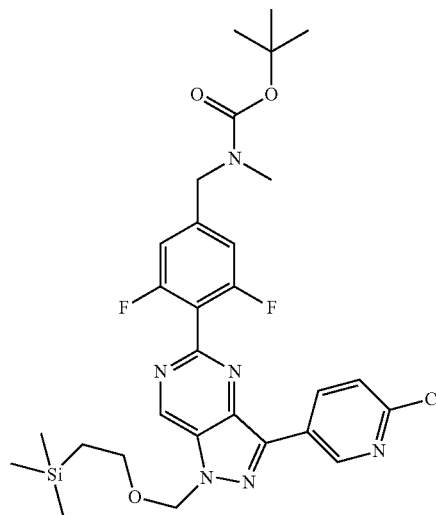
1-(4-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)piperazin-1-yl)-2-methylpropan-2-ol

[0644]



Step 1. tert-Butyl 4-(3-(6-chloropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-difluorobenzyl(methyl)carbamate

[0645]



[0646] To a solution of Intermediate 1 (500 mg, 0.792 mmol) in dioxane (6 ml) and water (1.5 ml) was added (6-chloropyridin-3-yl)boronic acid (112 mg, 0.713 mmol) followed by addition of potassium phosphate, tribasic (336 mg, 1.58 mmol). The resulting solution was degassed,  $PdCl_2(dppf)$  (64 mg, 0.079 mmol) was added and the reaction mixture was stirred at 90° C. for 2 hours. The reaction mixture was cooled to r.t. and concentrated to dryness. The residue was purified by silica gel chromatography using 0-100% ethyl acetate in hexanes to afford desired product as brownish oil (310 mg, 63.4%). LC-MS calculated for  $C_{29}H_{36}ClF_2N_6O_3Si$  (M+H)<sup>+</sup>: m/z=618.2; found 618.2.

Step 2. 1-(4-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)piperazin-1-yl)-2-methylpropan-2-ol

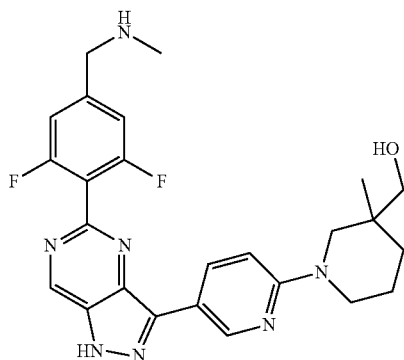
[0647] To a solution of tert-butyl 4-(3-(6-chloropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-difluorobenzyl(methyl)carbamate (100 mg, 0.162 mmol) in dioxane (5 mL) was added cesium carbonate (106 mg, 0.324 mmol) and 2-methyl-1-(piperazin-1-yl)propan-2-ol (128 mg, 0.810 mmol). The resulting mixture was degassed and chloro(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (12 mg, 0.016 mmol) was added. The resulting mixture was stirred at 90° C. for 2 hours. The reaction mixture was filtered, and 4.0 M HCl solution in dioxane (1 mL, 4.0 mmol) and 1 mL of water were added. The resulting mixture was stirred for another 1 hour at 80° C. 1 mL of methanol was added and the reaction mixture was stirred for another 30 mins at 80° C. The solution was then diluted with acetonitrile, filtered and then purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LC-MS calculated for  $C_{26}H_{31}F_2N_8O$  (M+H)<sup>+</sup>: m/z=509.2;

found 509.2.  $^1\text{H}$  NMR (600 MHz, DMSO)  $\delta$  9.54 (s, 1H), 9.22 (d,  $J=2.3$  Hz, 1H), 9.08 (bs, 1H), 8.50 (dd,  $J=8.9$ , 2.4 Hz, 1H), 7.46 (d,  $J=8.0$  Hz, 2H), 7.14 (d,  $J=8.9$  Hz, 1H), 4.31 (d,  $J=18.8$  Hz, 2H), 4.28 (t,  $J=5.6$  Hz, 2H), 3.71-3.61 (m, 2H), 3.59-3.49 (m, 2H), 3.30-3.21 (m, 2H), 3.20 (s, 2H), 2.65 (t,  $J=5.1$  Hz, 3H), 1.29 (s, 6H).

### Example 71

(1-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-3-methylpiperidin-3-yl)methanol

[0648]

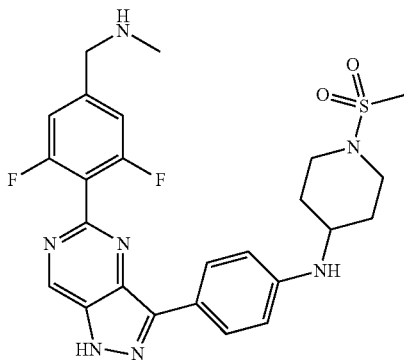


[0649] This compound was prepared according to the procedure described in Example 70, using (3-methylpiperidin-3-yl)methanol instead of 2-methyl-1-(piperazin-1-yl)propan-2-ol as starting material. LC-MS calculated for  $\text{C}_{25}\text{H}_{28}\text{F}_2\text{N}_7\text{O}$  ( $\text{M}+\text{H}^+$ ):  $m/z=480.2$ ; Found 480.2.

### Example 72

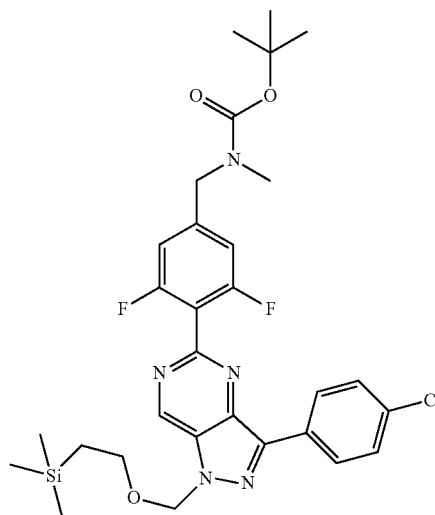
N-(4-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)-1-(methylsulfonyl)piperidin-4-amine

[0650]



Step 1. tert-Butyl 4-(3-(4-chlorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-difluorobenzyl(methyl)carbamate

[0651]



[0652] To a solution of Intermediate 1 (1 g, 1.583 mmol) in dioxane (12 ml) and water (3 ml) was added (4-chlorophenyl)boronic acid (173 mg, 1.11 mmol) followed by addition of potassium phosphate, tribasic (672 mg, 3.17 mmol). The resulting solution was degassed,  $\text{PdCl}_2(\text{dppf})$  (129 mg, 0.158 mmol) was added and the reaction mixture was stirred at  $90^\circ\text{C}$ . for 2 hours. The mixture was cooled to r.t. and then concentrated to dryness. The residue was purified by silica gel chromatography using 0-100% ethyl acetate in hexanes to afford desired product as brownish oil (450 mg, 46.1%). LC-MS calculated for  $\text{C}_{30}\text{H}_{37}\text{ClF}_2\text{N}_5\text{O}_3\text{Si}$  ( $\text{M}+\text{H}^+$ ):  $m/z=616.2$ ; found 616.2.

Step 2. N-(4-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)-1-(methylsulfonyl)piperidin-4-amine

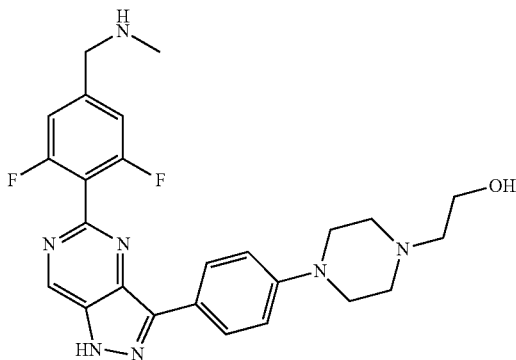
[0653] To a solution of tert-butyl 4-(3-(4-chlorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-difluorobenzyl(methyl)carbamate (30 mg, 0.049 mmol) in dioxane (1 ml) was added cesium carbonate (79 mg, 0.24 mmol) and 1-(methylsulfonyl)piperidin-4-amine (43.4 mg, 0.243 mmol). The mixture was degassed and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II) (7.66 mg, 9.74  $\mu\text{mol}$ ) was added. The resulting mixture was stirred at  $90^\circ\text{C}$ . for 2 hours. The mixture was filtered, and 4.0 M HCl solution in dioxane (1 mL, 4.0 mmol) and 1 mL of water were added. The reaction was stirred for another 1 hour at  $80^\circ\text{C}$ . 1 mL of methanol was added, and the reaction mixture was stirred for another 30 mins at  $80^\circ\text{C}$ . The solution was then diluted with acetonitrile, filtered and then purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LC-MS calculated for  $\text{C}_{25}\text{H}_{28}\text{F}_2\text{N}_7\text{O}_2\text{S}$  ( $\text{M}+\text{H}^+$ ):  $m/z=528.2$ ; found 528.2.



## Example 73

2-(4-(4-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperazin-1-yl)ethanol

[0654]

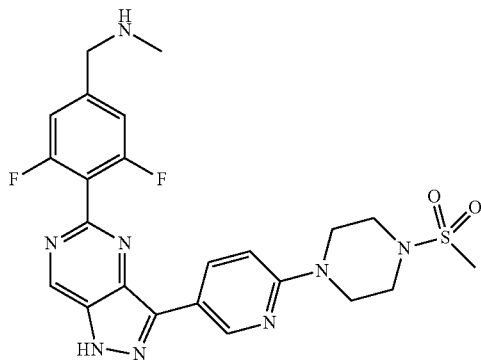


[0655] This compound was prepared according to the procedure described in Example 72, using 2-(piperazin-1-yl)ethanol instead of 1-(methylsulfonyl)piperidin-4-amine as starting material. LC-MS calculated for  $C_{25}H_{28}F_2N_7O$  ( $M+H$ )<sup>+</sup>:  $m/z=480.2$ ; Found 480.2. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  9.78 (s, 1H), 9.50 (s, 1H), 9.10 (s, 1H), 8.30 (d,  $J=8.5$  Hz, 2H), 7.53-7.38 (m, 2H), 7.23-7.12 (m, 2H), 4.27 (s, 2H), 3.94 (d,  $J=12.4$  Hz, 2H), 3.79 (t,  $J=5.2$  Hz, 2H), 3.68-3.56 (m, 3H), 3.27 (t,  $J=4.9$  Hz, 2H), 3.23-3.12 (m, 3H), 2.66 (s, 3H).

## Example 74

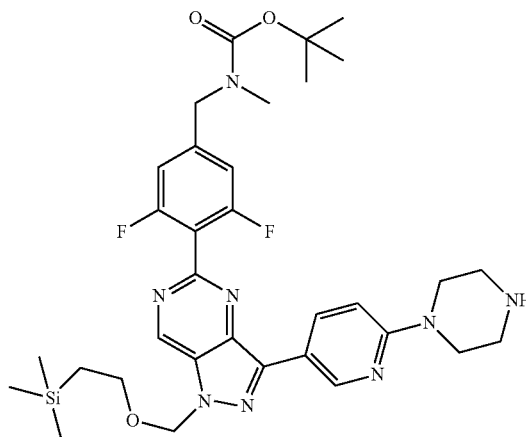
1-(3,5-Difluoro-4-(3-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0656]



Step 1. tert-Butyl 3,5-difluoro-4-(3-(6-(piperazin-1-yl)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzyl(methyl)carbamate

[0657]



[0658] To a solution of tert-butyl (3,5-difluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzyl)(methyl)carbamate (Intermediate 1, 300 mg, 0.475 mmol) in dioxane (3 mL) and water (0.750 mL) was added potassium phosphate, tribasic (202 mg, 0.950 mmol) and 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (165 mg, 0.570 mmol). The resulting mixture was degassed and chloro(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II) (74 mg, 0.095 mmol) was added. The resulting mixture was stirred at 90° C. for 2 hours. The mixture was concentrated to dryness. The residue was purified by silica gel chromatography using 0-10% methanol in DCM to afford desired product as brownish oil (220 mg, 69.5%). LC-MS calculated for  $C_{33}H_{45}F_2N_8O_3Si$  ( $M+H$ )<sup>+</sup>:  $m/z=667.2$ ; found 667.2.

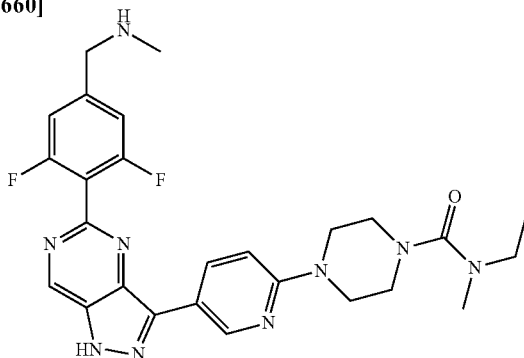
Step 2. 1-(3,5-Difluoro-4-(3-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0659] To a solution of tert-butyl (3,5-difluoro-4-(3-(6-(piperazin-1-yl)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzyl)(methyl)carbamate (25 mg, 0.037 mmol) in DCM (750  $\mu$ L) was added DIPEA (32.7  $\mu$ L, 0.187 mmol) followed by addition of methanesulfonyl chloride (22 mg, 0.19 mmol). The resulting solution was stirred at r.t. for 1 hour. 1 mL of TFA was added, and the reaction mixture was stirred at r.t. for another 1 hour. The solvent was then removed, and the residue was dissolved in methanol and stirred at 60° C. for 15 mins. The solution was diluted with acetonitrile, filtered and then purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LC-MS calculated for  $C_{23}H_{25}F_2N_8O_2S$  ( $M+H$ )<sup>+</sup>:  $m/z=515.2$ ; found 515.2.

## Example 75

4-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-N-ethyl-N-methylpiperazine-1-carboxamide

[0660]

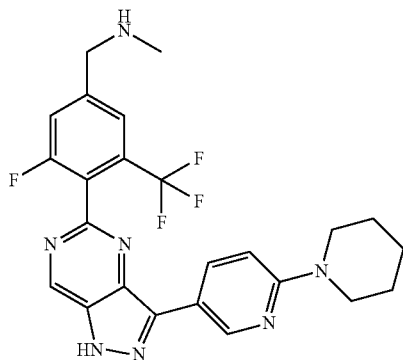


[0661] This compound was prepared according to the procedure described in Example 74, using ethyl(methyl) carbamic chloride instead of methanesulfonyl chloride as starting material. LC-MS calculated for  $C_{26}H_{30}F_2N_9O$  ( $M+H$ )<sup>+</sup>:  $m/z=522.2$ ; Found 522.2.

## Example 76

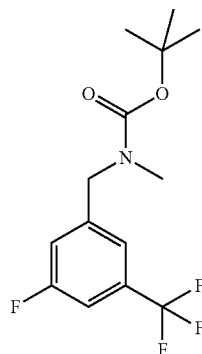
1-(3-Fluoro-4-(3-(6-(piperidin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)phenyl)-N-methylmethanamine

[0662]



Step 1. tert-Butyl 3-fluoro-5-(trifluoromethyl)benzyl(methyl)carbamate

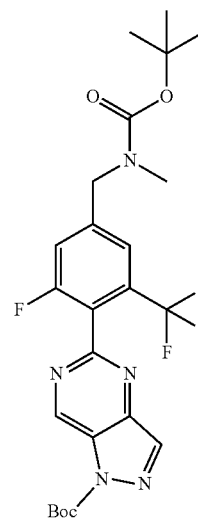
[0663]



[0664] To a solution of 3-fluoro-5-(trifluoromethyl)benzaldehyde (20.0 g, 104 mmol) in MeOH (500 ml) was added methylamine solution (104 ml, 208 mmol, 2M in THF) and the reaction mixture was stirred at r.t. for 1 hour. Sodium borohydride (7.88 g, 208 mmol) was added, and the reaction mixture was stirred for additional 30 mins. The mixture was concentrated to dryness and 300 mL of DCM was added. Aqueous solution of sodium bicarbonate was added, and the reaction mixture was stirred at r.t. for another 1 hour. The organic layer was separated, and it was dried over  $MgSO_4$ , filtered and concentrated to dryness. To a solution of the resulting residue in DCM (521 ml) was added triethylamine (14.5 ml, 104 mmol) and di-tert-butyl dicarbonate (22.7 g, 104 mmol). The resulting solution was stirred at r.t. for 1 hour. After this time it was concentrated to dryness and the residue was purified by silica gel chromatography using 0-70% ethyl acetate in hexanes to afford desired product as colorless oil (15.1 g, 47.0%). LC-MS calculated for  $C_{10}H_{10}F_4NO_2$  ( $M+H$ — $C_4H_8$ )<sup>+</sup>: 252.1; found 252.2.

Step 2. tert-Butyl 5-(4-((tert-butoxycarbonyl(methyl)amino)methyl)-2-fluoro-6-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

[0665]

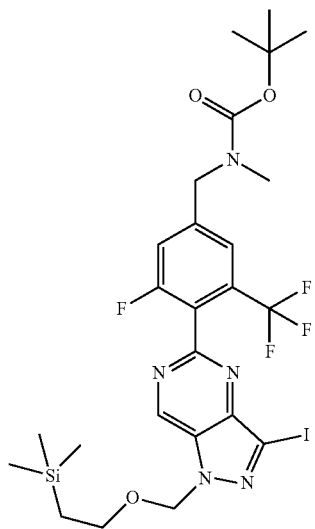


[0666] To a solution of tert-butyl (3-fluoro-5-(trifluoromethyl)benzyl)(methyl)carbamate (2.3 g, 7.5 mmol) in THF (33.3 ml) was added n-butyllithium (8.98 ml, 22.5 mmol) dropwise at  $-78^\circ C$ , and the reaction mixture was stirred at  $-78^\circ C$  for 1 hour. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.57 g, 29.9 mmol) was added. The resulting mixture was allowed to warm up to r.t. over 1 hour. The resulting solution was quenched with water, neutralized to pH=6, and the desired product was extracted with ethyl acetate. The organic layer was washed with brine, dried over  $MgSO_4$ , filtered and then concentrated to dryness. To a solution of the resulting residue in dioxane (33.3 ml) and water (8.32 ml) was added potassium phosphate (1.30 g, 7.48 mmol) and tert-butyl 5-chloro-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (0.953 g, 3.74 mmol). The mixture was degassed with  $N_2$ , chloro(2-dicyclohexylphosphino)-2',

4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II) (0.118 g, 0.150 mmol) was added, and the reaction mixture was stirred at 60° C. for 1 hour. After this time it was concentrated to dryness. The residue was purified by silica gel chromatography using 0-100% ethyl acetate in hexanes to afford desired product as yellowish oil (850 mg, 43.2%). LC-MS calculated for  $C_{24}H_{28}F_4N_5O_4$  (M+H)<sup>+</sup>: m/z=526.2; Found 526.2.

Step 3. tert-Butyl 3-fluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)benzyl(methyl)carbamate

[0667]



[0668] To a solution of tert-butyl 5-(4-(((tert-butoxycarbonyl)(methyl)amino)methyl)-2-fluoro-6-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (250 mg, 0.476 mmol) in dioxane (2.5 ml) and water (2.5 ml) was added potassium carbonate (329 mg, 2.38 mmol), and the reaction mixture was stirred at 80° C. for 2 hours. The mixture was cooled to r.t., diluted with DCM and washed with water, sodium bicarbonate and brine. The organic layer was dried over  $MgSO_4$ , filtered and then concentrated to dryness. To a solution of the resulting residue in acetonitrile (5 ml) was added N-iodosuccinimide (91 mg, 0.40 mmol) and the reaction was stirred at 50° C. for 1 hour. The mixture was cooled to r.t., DIPEA (83  $\mu$ l, 0.476 mmol) was added followed by the dropwise addition of SEM-Cl (71.7  $\mu$ l, 0.404 mmol). The resulting solution was stirred at r.t. for 30 mins, then concentrated to dryness. The residue was purified by silica gel chromatography using 0-70% ethyl acetate in hexanes to afford desired product as dark brownish solid (260 mg, 80.0%). LC-MS calculated for  $C_{25}H_{33}F_4IN_5O_3Si$  (M+H)<sup>+</sup>: m/z=682.2; found 682.2.

Step 4. 1-(3-Fluoro-4-(3-(6-(piperidin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)phenyl)-N-methylmethanamine

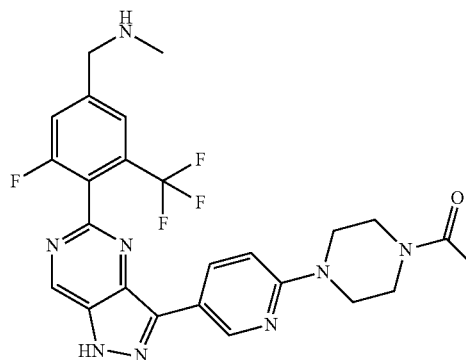
[0669] To a solution of tert-butyl (3-fluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)benzyl(methyl)carbamate (20 mg, 0.029 mmol) in dioxane (800  $\mu$ l) and water (200  $\mu$ l) was added (6-(piperidin-1-yl)pyridin-3-yl)boronic acid (6.1

mg, 0.029 mmol) followed by the addition of potassium phosphate, tribasic (12.4 mg, 0.058 mmol). The resulting solution was degassed,  $PdCl_2(dppf)$  (2.4 mg, 2.93  $\mu$ mol) was added, and the reaction mixture was stirred at 90° C. for 2 hours. The mixture was cooled to r.t. and then HCl, 4.0 M in dioxane (1 ml, 4.00 mmol) was added, followed by the addition of 1 ml of water. The resulting solution was stirred at 80° C. for 2 hours. The solution was cooled to r.t., diluted with acetonitrile, filtered and purified by prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LC-MS calculated for  $C_{24}H_{24}F_4N_7$  (M+H)<sup>+</sup>: m/z=486.2; found 486.2.

Example 77

1-(4-(5-(5-(2-Fluoro-4-((methylamino)methyl)-6-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)piperazin-1-yl)ethanone

[0670]

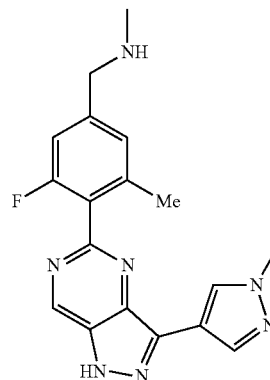


[0671] This compound was prepared according to the procedure described in Example 76, using 6-(4-acetylpiperazin-1-yl)pyridin-3-ylboronic acid instead of (6-(piperidin-1-yl)pyridin-3-yl)boronic acid as starting material. LC-MS calculated for  $C_{25}H_{25}F_4N_8O$  (M+H)<sup>+</sup>: m/z=529.2; Found 529.2.

Example 78

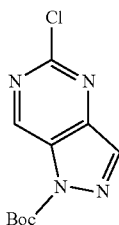
1-(3-Fluoro-5-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0672]



Step 1. tert-Butyl 5-chloro-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

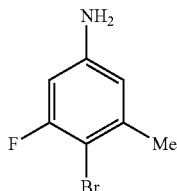
[0673]



[0674] In a 50 mL round-bottom flask with a stir bar, 5-chloro-1H-pyrazolo[4,3-d]pyrimidine (Oxchem, 600 mg, 3.88 mmol) and triethylamine (649  $\mu$ L, 4.66 mmol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (12.9 mL). Di-tert-butyl dicarbonate (991  $\mu$ L, 4.27 mmol) was added, and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was then diluted with water, extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (860 mg, 87%). LCMS calculated for  $\text{C}_{10}\text{H}_{12}\text{ClN}_4\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$   $m/z$ =255.1; found 255.2.

Step 2. 4-Bromo-3-fluoro-5-methylaniline

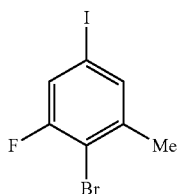
[0675]



[0676] N-Bromosuccinimide (15.8 g, 89 mmol) was added to a solution of 3-fluoro-5-methylaniline (Combi-Blocks, 11 g, 88 mmol) in DMF (80 mL) cooled to 0° C. in an ice bath. The reaction mixture was stirred at 0° C. for 30 minutes. After warming to r.t., the reaction was stirred for an additional 1 hour. Water and EtOAc were then added, and the organic phase was washed with saturated aqueous  $\text{NaHCO}_3$  and brine. The organic phase was then dried over magnesium sulfate and the solvents were evaporated under reduced pressure. The crude product was purified by Biotage Isolera™ (17.2 g, 96%). LCMS calculated for  $\text{C}_7\text{H}_8\text{BrFN}$  ( $\text{M}+\text{H}$ ) $^+$   $m/z$ =203.9; found 204.0.

Step 3. 2-Bromo-1-fluoro-5-iodo-3-methylbenzene

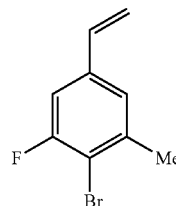
[0677]



[0678] To a solution of 4-bromo-3-fluoro-5-methylaniline (7.28 g, 36 mmol) in acetonitrile (190 mL) cooled to 0° C. in an ice bath was added sulfuric acid (4.75 mL, 89 mmol) dissolved in  $\text{H}_2\text{O}$  (10 mL). After stirring for 5 minutes, a solution of sodium nitrite (4.92 g, 71.4 mmol) in water (10 mL) was added dropwise, and the reaction mixture was stirred for an additional 15 minutes at 0° C. Potassium iodide (23.7 g, 143 mmol) in water (20 mL) was then added, and the ice-bath was removed. After warming to r.t., the reaction was stirred for an additional 20 minutes before the reaction was quenched via the addition of aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was then extracted with ethyl acetate and the combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (10.3 g, 94%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (br s, 1H), 7.29 (m, 1H), 2.38 (s, 3H) ppm.

Step 4. 2-Bromo-1-fluoro-3-methyl-5-vinylbenzene

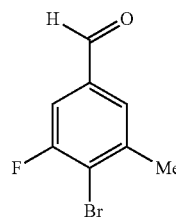
[0679]



[0680] To a solution of 2-bromo-1-fluoro-5-iodo-3-methylbenzene (10.3 g, 32.8 mmol) in 1,4-dioxane (80 mL) and water (13.3 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, 6.16 mL, 34.5 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ( $\text{Pd}(\text{dppf})\text{Cl}_2$ ) (2.40 g, 3.3 mmol), and potassium phosphate tribasic (13.9 g, 65.7 mmol). The reaction mixture was degassed with nitrogen and heated to 70° C. for 1 h. After cooling to r.t., the reaction was filtered over a pad of Celite, diluted with water, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (5.46 g, 77%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.05 (br s, 1H), 7.01 (dd,  $J$ =2.0, 9.4 Hz, 1H), 6.60 (dd,  $J$ =10.9, 17.5 Hz, 1H), 5.75 (d,  $J$ =17.5 Hz, 1H), 5.31 (d,  $J$ =10.9 Hz, 1H), 2.42 (s, 3H) ppm.

Step 5. 4-Bromo-3-fluoro-5-methylbenzaldehyde

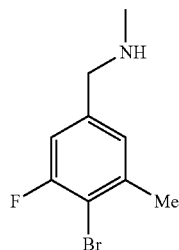
[0681]



**[0682]** To a solution of 2-bromo-1-fluoro-3-methyl-5-vinylbenzene (5.46 g, 25.4 mmol) in acetone (46 mL) and water (4.6 mL) was sequentially added sodium periodate (21.7 g, 102 mmol) and a 4% aqueous solution of osmium tetroxide (8.07 mL, 1.27 mmol). The reaction was stirred at r.t. for 2 h. The reaction mixture was then filtered over a pad of celite, diluted with water, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (3.22 g, 58%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.93 (d, J=1.8 Hz, 1H), 7.55 (d, J=1.8 Hz, 1H), 7.44 (dd, J=1.8, 7.8 Hz, 1H), 2.52 (s, 3H) ppm.

Step 6. 1-(4-Bromo-3-fluoro-5-methylphenyl)-N-methylmethanamine

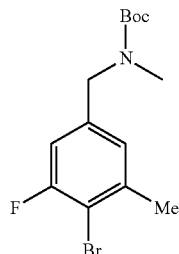
**[0683]**



**[0684]** In a 20 mL scintillation vial equipped with a magnetic stir bar, 4-bromo-3-fluoro-5-methylbenzaldehyde (1.46 g, 6.70 mmol) was dissolved in MeOH (6.70 mL) and the reaction was placed under a nitrogen environment. Following this, a 33% solution of methanamine (3.15 g, 33.5 mmol) in ethanol and titanium(IV) isopropoxide (0.982 mL, 3.35 mmol) were added, and the reaction mixture was stirred at r.t. for 3 hours. Sodium borohydride (1.01 g, 26.8 mmol) was then added to the reaction mixture portion wise and stirring was continued at r.t. for an additional 1.5 hours. NH<sub>4</sub>OH (30% aqueous solution) was added to the reaction mixture and stirring continued for another 15 minutes. The reaction was then acidified with 1 N HCl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to afford 1-(4-bromo-3-fluoro-5-methylphenyl)-N-methylmethanamine (1.32 g, 85%) as a light yellow oil. The crude product was used in the next step without further purification. LCMS calculated for C<sub>9</sub>H<sub>12</sub>BrFN (M+H)<sup>+</sup> m/z=232.0; found 231.9.

Step 7. tert-Butyl 4-bromo-3-fluoro-5-methylbenzyl(methyl)carbamate

**[0685]**

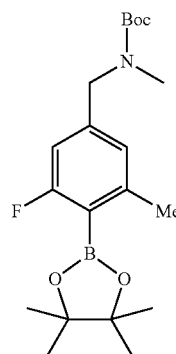


**[0686]** To a solution of 1-(4-bromo-3-fluoro-5-methylphenyl)-N-methylmethanamine (1.32 g, 5.67 mmol) and triethylamine (1.58 mL, 11.34 mmol) in THF (18.9 mL) was added di-tert-butyl dicarbonate (1.58 mL, 6.80 mmol). The

reaction mixture was then stirred at ambient temperature for 1 hour. The reaction mixture was then diluted with water and extracted with ethyl acetate. The combined organic layers were then dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (1.42 g, 78%). LCMS calculated for C<sub>10</sub>H<sub>12</sub>BrFNO<sub>2</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup> m/z=276.0; found 276.0.

Step 8. tert-Butyl 3-fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl(methyl)carbamate

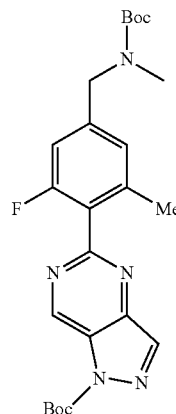
**[0687]**



**[0688]** In an oven-dried 20 mL scintillation vial with a stir bar, tert-butyl (4-bromo-3-fluoro-5-methylbenzyl)(methyl)carbamate (573 mg, 1.73 mmol) was dissolved in THF (11.5 mL). The reaction mixture was then cooled to -78° C. in a dry ice/acetone bath and n-BuLi (1.6 M solution in hexanes, 1.19 mL, 1.90 mmol) was added dropwise. The reaction mixture was then allowed to stir for 3 minutes before 2-isopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (427 μL, 2.25 mmol) was added dropwise. The mixture was warmed to r.t and stirred for an additional 5 hours. The reaction mixture was quenched by the addition of water, acidified to pH 5-6 using 1 N HCl, and extracted with ethyl acetate. The combined organic layers were then washed with brine, dried over magnesium sulfate, and concentrated to afford tert-butyl 3-fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl(methyl)carbamate. The crude product was used in the next step without further purification. LCMS calculated for C<sub>16</sub>H<sub>24</sub>BrFNO<sub>4</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup> m/z=324.2; found 324.1.

Step 9. tert-Butyl 5-(4-((tert-butoxycarbonyl(methyl)amino)methyl)-2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

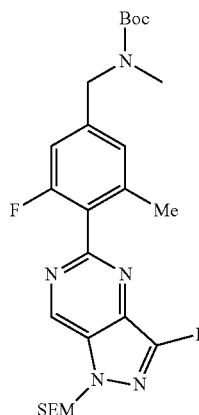
**[0689]**



**[0690]** In a 20 mL scintillation vial equipped with a magnetic stir bar, tert-butyl 5-chloro-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (340 mg, 1.34 mmol) and tert-butyl (3-fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)(methyl)carbamate (557 mg, 1.47 mmol) were dissolved in 1,4-dioxane (8.0 mL) and water (2.0 mL). To this mixture was added chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (Pd XPhos G2) (158 mg, 0.20 mmol) and potassium phosphate tribasic (567 mg, 2.67 mmol). The reaction mixture was then degassed by bubbling nitrogen through the resulting mixture, and the reaction mixture was sealed and heated to 75° C. for 1 h. After cooling to r.t., the reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (532 mg, 84%). LCMS calculated for C<sub>24</sub>H<sub>31</sub>FN<sub>5</sub>O<sub>4</sub> (M+H)<sup>+</sup> m/z=472.2; found 472.3.

Step 10. tert-Butyl 3-fluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-methylbenzyl(methyl)carbamate

**[0691]**



**[0692]** In a 20 mL scintillation vial with a stir bar, tert-butyl 5-(4-(((tert-butoxycarbonyl)(methyl)amino)methyl)-2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (817 mg, 1.73 mmol) and potassium carbonate (958 mg, 6.93 mmol) were dissolved in 1,4-dioxane (6.06 mL) and water (6.06 mL). The reaction was then purged under a nitrogen environment and heated to 80° C. for 2 hours. The reaction was diluted with water and extracted with ethyl acetate. The combined organic phases were then washed with brine, dried over magnesium sulfate, and concentrated. The crude intermediate was dissolved in acetonitrile (10 mL) and N-iodosuccinimide (507 mg, 2.25 mmol) was added, and the reaction mixture heated to 60° C. for 1 hour. N,N-diisopropylethylamine (393 µL, 2.25 mmol) and [2-(trimethylsilyl)ethoxy]methyl chloride (369 µL, 2.08 mmol) were added to the reaction mixture was stirred at r.t. for an additional 1 h. The reaction mixture was then concentrated under reduced pressure and the crude product was purified by Biotage Isolera™ (412 mg, 38%). LCMS calculated for C<sub>25</sub>H<sub>36</sub>FIN<sub>5</sub>O<sub>3</sub>Si (M+H)<sup>+</sup> m/z=628.2; found 628.1.

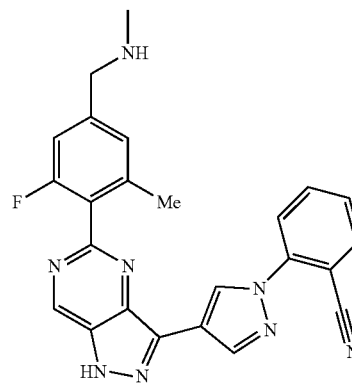
Step 11. 1-(3-Fluoro-5-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

**[0693]** In a 4 dram vial equipped with a magnetic stir bar, tert-butyl (3-fluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-methylbenzyl)(methyl)carbamate (20 mg, 0.032 mmol) was dissolved in 1,4-dioxane (0.5 mL) and water (0.08 mL). To this solution was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (9.28 mg, 0.045 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (Pd XPhos G2) (2.5 mg, 0.0032 mmol), and potassium phosphate (13.5 mg, 0.064 mmol). The reaction mixture was then degassed, sealed, and stirred at 85° C. for 1 h. The reaction was then concentrated and CH<sub>2</sub>Cl<sub>2</sub> (0.25 mL) followed by TFA (0.25 mL) were added, and the mixture was stirred at 30° C. for 90 minutes. The reaction was then concentrated and methanol (1.0 mL) followed by 7 drops of NH<sub>4</sub>OH (30% aqueous solution) was added and stirring was continued at 30° C. for 1 hour. The reaction mixture was then concentrated, dissolved in methanol and purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS calculated for C<sub>18</sub>H<sub>19</sub>FN<sub>7</sub> (M+H)<sup>+</sup>: m/z=352.2; Found: 352.2.

#### Example 79

2-(4-(5-(2-Fluoro-6-methyl-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile

**[0694]**



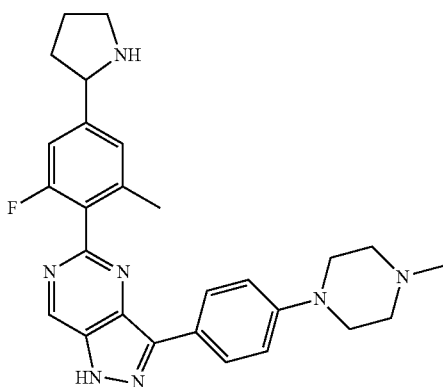
**[0695]** In a 4 dram vial equipped with a magnetic stir bar, tert-butyl (3-fluoro-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-methylbenzyl)(methyl)carbamate (18.9 mg, 0.030 mmol) was dissolved in 1,4-dioxane (0.5 mL) and water (0.08 mL). To this solution was added 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)benzonitrile (12.4 mg, 0.042 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (Pd XPhos G2) (3.6 mg, 0.0032 mmol), and potassium phosphate (16.0 mg, 0.064 mmol). The reaction mixture was then degassed, sealed, and stirred at 80° C. for 1 h. Following this, a 4 N solution of HCl in 1,4-dioxane (2 mL) was

added and the reaction was stirred at r.t. for 1 hour. The reaction mixture was then concentrated, dissolved in methanol and purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS calculated for  $C_{24}H_{20}FN_8$  (M+H)<sup>+</sup>: m/z=439.2; Found: 439.1.

## Example 80

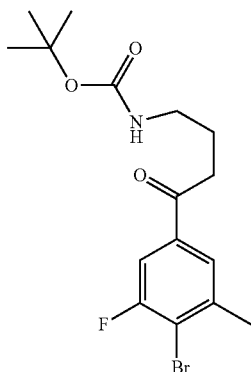
5-(2-Fluoro-6-methyl-4-(pyrrolidin-2-yl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0696]



Step 1. tert-Butyl 4-(4-bromo-3-fluoro-5-methylphenyl)-4-oxobutylcarbamate

[0697]

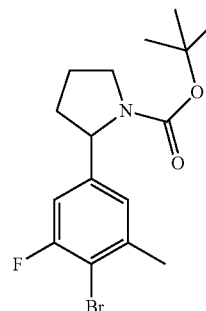


[0698] To a solution of 2-bromo-1-fluoro-5-iodo-3-methylbenzene (1.34 g, 4.25 mmol, Example 78, Step 3) in THF (30 mL) was added a solution of isopropylmagnesium chloride in THF (2.13 mL, 4.25 mmol, 2 M) dropwise at -40 °C. After stirring at -40 °C. for 1 h, the mixture was cooled to -78 °C. and tert-butyl 2-oxopyrrolidine-1-carboxylate (0.726 mL, 4.25 mmol) was added. The mixture was then slowly warmed to RT over 1.5 h. The mixture was quenched by 1 M HCl, extracted with ethyl acetate and concentrated in vacuo. The obtained crude product was purified by

Biotage Isolera™ to give the desired product. LCMS calculated for  $C_{11}H_{14}BrFNO$  (M-Boc+2H)<sup>+</sup>: m/z=274.0; Found: 274.0.

Step 2. tert-Butyl 2-(4-bromo-3-fluoro-5-methylphenyl)pyrrolidine-1-carboxylate

[0699]



[0700] To a solution of tert-butyl 4-(4-bromo-3-fluoro-5-methylphenyl)-4-oxobutylcarbamate (1.30 g, 3.47 mmol) in DCM (15 mL) was added 15 mL TFA, and the mixture was stirred at RT for 30 min. The mixture was concentrated in vacuo and then dissolved in 30 mL THF. To this solution was added triethylamine (0.593 mL, 4.25 mmol) and sodium triacetoxyborohydride (1.80 g, 8.51 mmol). The mixture was stirred at RT for 18 h and then quenched by 1 M NaOH. The mixture was extracted by ethyl acetate and concentrated in vacuo. The obtained crude product was dissolved in THF (20 mL). To this solution was added di-tert-butyl dicarbonate (1.86 g, 8.51 mmol) and triethylamine (0.513 mL, 3.68 mmol) at RT. After stirring for 1 h, the solvents were evaporated under reduced pressure and the obtained crude product was purified by Biotage Isolera™ to give the desired product. LCMS calculated for  $C_{12}H_{14}BrFNO_2$  (M-C<sub>4</sub>H<sub>8</sub>+H)<sup>+</sup>: m/z=302.0; Found: 302.0.

Step 3. 5-(2-Fluoro-6-methyl-4-(pyrrolidin-2-yl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

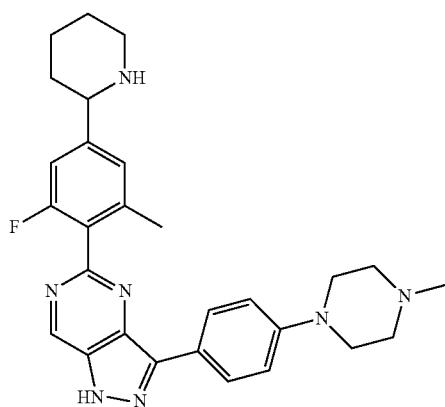
[0701] A mixture of tert-butyl 2-(4-bromo-3-fluoro-5-methylphenyl)pyrrolidine-1-carboxylate (65 mg, 0.181 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (69.1 mg, 0.272 mmol), potassium acetate (53.4 mg, 0.544 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) complex with dichloromethane (1:1) (29.6 mg, 0.036 mmol) in dioxane (10 mL) was stirred at 110 °C. for 24 h. After cooling to room temperature, the mixture was concentrated in vacuo. A mixture of this crude material, 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (25.8 mg, 0.056 mmol, Example 1, Step 3), XPhos Pd G2 (4.14 mg, 5.61 μmol) and cesium carbonate (54.9 mg, 0.168 mmol) in dioxane (10 mL) and water (2 mL) was stirred at 70 °C. for 18 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude mixture was then dissolved in DCM (2.0 mL) and TFA (2.0 mL) was added dropwise at room temperature. After stirring for 2 h, the mixture was concentrated in vacuo. The crude mixture was dissolved in MeOH (3.5 mL) and 10% aqueous NH<sub>4</sub>OH

(1.5 mL) was added. The mixture was purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to give the desired product. LCMS calculated for  $C_{27}H_{31}FN_7$  (M+H)<sup>+</sup>: m/z=472.3; Found: 472.3.

### Example 81

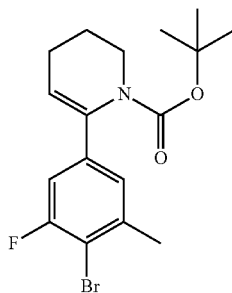
5-(2-Fluoro-6-methyl-4-(piperidin-2-yl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0702]



Step 1. tert-Butyl 6-(4-bromo-3-fluoro-5-methylphenyl)-3,4-dihydropyridine-1(2H)-carboxylate

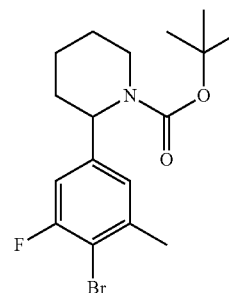
[0703]



[0704] A solution of 2-bromo-1-fluoro-5-iodo-3-methylbenzene (526 mg, 1.67 mmol, Example 78, Step 3), tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2H)-carboxylate (516 mg, 1.67 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium (II) complex with dichloromethane (1:1) (136 mg, 0.167 mmol) and potassium carbonate (461 mg, 3.34 mmol) in dioxane (10 mL) and water (2 mL) was stirred at 65° C. for 18 h. After cooling to room temperature, the mixture was concentrated in vacuo. The obtained crude product was purified by Biotage Isolera™ to give the desired product. LCMS calculated for  $C_{13}H_{14}BrFNO_2$  (M-C<sub>4</sub>H<sub>8</sub>+H)<sup>+</sup>: m/z=314.0; Found: 313.9.

Step 2. tert-Butyl 2-(4-bromo-3-fluoro-5-methylphenyl)piperidine-1-carboxylate

[0705]



[0706] To a solution of tert-butyl 6-(4-bromo-3-fluoro-5-methylphenyl)-3,4-dihydropyridine-1(2H)-carboxylate (530 mg, 1.42 mmol) in DCM (10 mL) was added 10 mL TFA, and the mixture was stirred at RT for 30 min. The mixture was concentrated in vacuo and then dissolved in 20 mL THF. To this solution was added triethylamine (0.233 mL, 1.67 mmol) and sodium triacetoxyborohydride (707 mg, 3.34 mmol). The mixture was stirred at RT for 18 h and then quenched by 1 M NaOH. The mixture was extracted by ethyl acetate and concentrated in vacuo. The obtained crude product was dissolved in THF (20 mL). To this solution was added di-tert-butyl dicarbonate (364 mg, 1.67 mmol) at RT. After stirring for 3 h, the solvents were evaporated under reduced pressure and the obtained crude product was purified by Biotage Isolera to give the desired product. LCMS calculated for  $C_{13}H_{16}BrFNO_2$  (M-C<sub>4</sub>H<sub>8</sub>+H)<sup>+</sup>: m/z=316.0; Found: 315.9.

Step 3. 5-(2-Fluoro-6-methyl-4-(piperidin-2-yl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0707] A mixture of tert-butyl 2-(4-bromo-3-fluoro-5-methylphenyl)piperidine-1-carboxylate (65 mg, 0.175 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (66.5 mg, 0.262 mmol), potassium acetate (51.4 mg, 0.524 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) complex with dichloromethane (1:1) (28.5 mg, 0.035 mmol) in dioxane (10 mL) was stirred at 105° C. for 24 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude boronic ester intermediate was treated with 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (24.9 mg, 0.054 mmol, Example 1, Step 3), XPhos Pd G2 (4.0 mg, 5.43 μmol) and cesium carbonate (53.0 mg, 0.163 mmol) in dioxane (10 mL)/water (2 mL) and stirred at 70° C. for 18 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude Pd coupling product mixture was then dissolved in DCM (2.0 mL) and treated with TFA (2.0 mL) dropwise at room temperature. After stirring for 2 h, the mixture was concentrated in vacuo. The crude product mixture was dissolved in MeOH (3.5 mL) and 10% aqueous NH<sub>4</sub>OH (1.5 mL) was added. The mixture was purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60

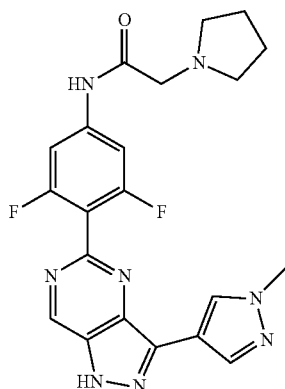


mL/min) to give the desired product. LCMS calculated for  $C_{28}H_{33}FN_7$  (M+H)<sup>+</sup>: m/z=486.3; Found: 486.4.

### Example 82

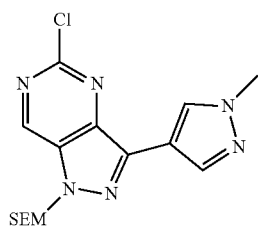
N-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide

[0708]



Step 1. 5-Chloro-3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine

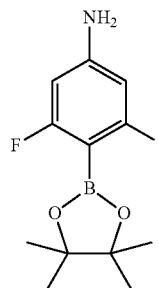
[0709]



[0710] To a mixture of 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (3.25 g, 7.91 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.646 g, 7.91 mmol), dppf-PdCl<sub>2</sub> (0.323 g, 0.396 mmol) and potassium carbonate (2.187 g, 15.83 mmol) were added 1,4-dioxane (15.83 ml) and water (3.96 ml), and the reaction flask was evacuated, back filled with nitrogen, then stirred at 90° C. overnight. The mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and purified by Biotage Isolera™ (flash purification system with ethyl acetate/hexanes at a ratio from 0 to 100%) to provide the desired product as a dark oil (2.08 g, 72%). LC-MS calculated for  $C_{15}H_{22}ClN_6OSi$  [M+H]<sup>+</sup> m/z: 365.2, found 365.2.

Step 2. 3,5-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

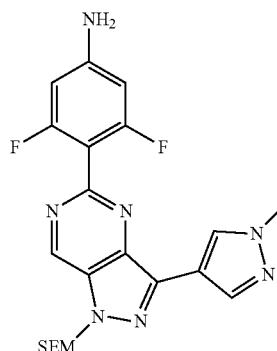
[0711]



[0712] To a mixture of 4-bromo-3,5-difluoroaniline (3.30 g, 15.9 mmol), dppf-PdCl<sub>2</sub> (0.648 g, 0.793 mmol), bis(pinacolato)diboron (6.04 g, 23.8 mmol) and potassium acetate (3.11 g, 31.7 mmol) was added 1,4-dioxane (31.7 ml) and the reaction flask was evacuated, back filled with nitrogen, then stirred at 100° C. overnight. The reaction mixture was then diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and purified by Biotage Isolera™ (flash purification system with ethyl acetate/hexanes at a ratio from 0 to 100%) to provide the desired product as a brown solid (2.4 g, 59%). LC-MS calculated for  $C_{12}H_{17}BF_2NO_2$  [M+H]<sup>+</sup> m/z: 256.1, found 256.1.

Step 3. Preparation of 3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)aniline

[0713]

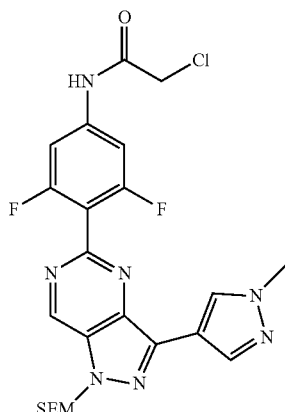


[0714] To a mixture of 5-chloro-3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (475 mg, 1.302 mmol), 3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (432 mg, 1.692 mmol), Xphos Pd G2 (102 mg, 0.130 mmol) and potassium phosphate, tribasic (553 mg, 2.60 mmol) were added 1,4-dioxane (4.75 ml) and water (0.950 ml) and the reaction mixture was evacuated, back filled with nitrogen, then stirred at 80° C. for 1 hr. The mixture was then diluted with DCM and filtered through a plug of Celite. The filtrate was concentrated and purified by Biotage Isolera™ (flash purification system with dichloromethane/methanol at a

ratio from 2 to 10%) to provide the desired product as a brown solid. LC-MS calculated for  $C_{21}H_{26}F_2N_7OSi$   $[M+H]^+$  m/z: 458.2, found 458.2.

Step 4. Preparation of 2-chloro-N-(3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)acetamide

[0715]



[0716] To a mixture of 3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)aniline (100 mg, 0.219 mmol), 2-chloroacetic acid (41.3 mg, 0.437 mmol) and HATU (125 mg, 0.328 mmol) in DMF (1093  $\mu$ l) was added Hunig's base (115  $\mu$ l, 0.656 mmol) and the reaction mixture stirred at r.t. for 1 hr. The mixture was then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. The residue was used in the next step without further purification. LC-MS calculated for  $C_{23}H_{27}ClF_2N_7O_2Si$   $[M+H]^+$  m/z: 534.2, found 534.2.

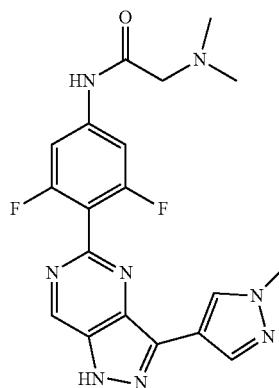
Step 5. Preparation of N-(3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide

[0717] To a solution of 2-chloro-N-(3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)acetamide (25 mg, 0.047 mmol) in DMF (468  $\mu$ l) was added pyrrolidine (7.83  $\mu$ l, 0.094 mmol) and the reaction mixture was stirred at 80° C. for 2 hrs. It was then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. To the residue were added methanol (1 mL) and 4N HCl (1 mL) and the reaction mixture heated to 80° C. for 30 mins, then cooled to r.t., diluted with methanol and purified directly on prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to provide the desired product. LC-MS calculated for  $C_{21}H_{21}F_2N_8O$   $[M+H]^+$  m/z: 439.2, found 439.2.

#### Example 83

N-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-2-(dimethylamino)acetamide

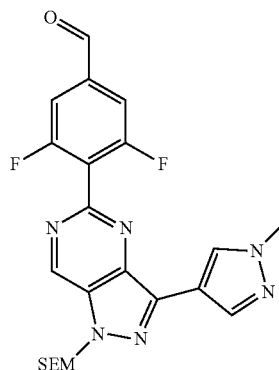
[0718]



[0719] This compound was prepared using procedures analogous to those for example 82, with dimethyl amine replacing pyrrolidine. LCMS calculated for  $C_{19}H_{19}F_2N_8O$   $[M+H]^+$  m/z: 413.2; Found: 413.2.

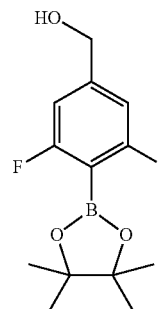
Preparation of 3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzaldehyde

[0720]



Step 1. Preparation of (3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol

[0721]

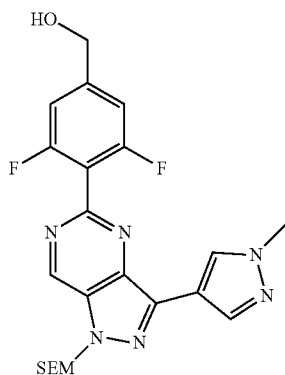


[0722] To a solution of 3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (4.0 g, 14.92

mmol) in tetrahydrofuran (149 ml) was added sodium borohydride (0.677 g, 17.91 mmol). After 2 hrs, the reaction was quenched with sat. sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was used in the next step without further purification.

Step 2. Preparation of (3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)methanol

[0723]



[0724] To a mixture of 5-chloro-3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (425 mg, 1.165 mmol), (3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (472 mg, 1.747 mmol), Xphos Pd G2 (92 mg, 0.116 mmol) and potassium phosphate (494 mg, 2.329 mmol) were added 1,4-dioxane (3 ml) and water (776  $\mu$ l), and the reaction flask was evacuated, back filled with nitrogen, then stirred at 95° C. for 2 hrs. The mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and purified by Biotage Isolera™ (flash purification system with dichloromethane/methanol at a ratio from 2 to 10%) to provide the desired product as a dark oil. LCMS calculated for  $C_{22}H_{27}F_2N_6O_2Si$  [M+H]<sup>+</sup> m/z: 473.2; Found: 473.2.

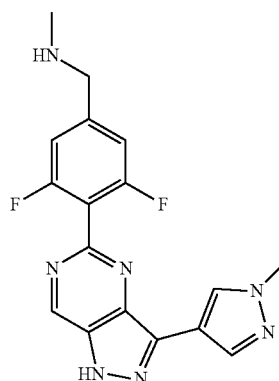
Step 3. Preparation of 3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzaldehyde

[0725] To a solution of (3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)methanol (550 mg, 1.164 mmol) in DCM (6 mL) was added manganese dioxide (1.9 g, 22.11 mmol). The reaction mixture was heated to 60° C. for 1 hr, and then filtered through a plug of Celite. The filtrate was concentrated and purified by Biotage Isolera™ (flash purification system with hexanes/ethyl acetate at a ratio from 0 to 100%) to provide the desired product as an oil. LCMS calculated for  $C_{22}H_{25}F_2N_6O_2Si$  [M+H]<sup>+</sup> m/z: 471.2; Found: 471.2.

#### Example 84

1-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0726]

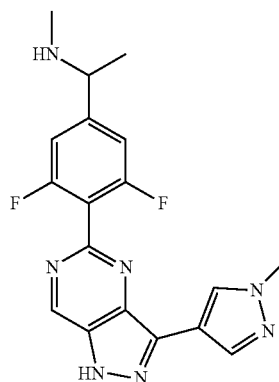


[0727] To a solution of 3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzaldehyde (25 mg, 0.053 mmol) and methanamine (2M in THF, 0.133 ml, 0.266 mmol) in toluene (1 ml) was added acetic acid (9.12  $\mu$ l, 0.159 mmol) and the reaction mixture was stirred at 80° C. overnight. The mixture was then concentrated and redissolved in methanol (1 mL). Sodium borohydride (2.010 mg, 0.053 mmol) was then added and the mixture was stirred at r.t. for 30 mins. Then 4 N HCl in dioxane was added (1 mL), and the reaction mixture was heated to 80 degrees for 30 mins. The mixture was then diluted with methanol and purified directly on prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to provide the desired product. LC-MS calculated for  $C_{17}H_{16}F_2N_7$  [M+H]<sup>+</sup> m/z: 356.2, found 356.2.

#### Example 85

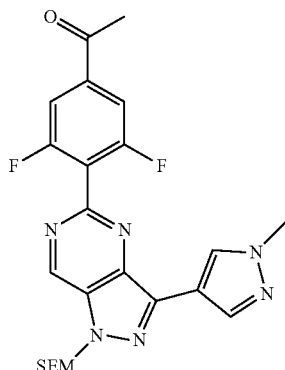
1-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0728]



Step 1. 1-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)ethanone

[0729]



[0730] To a solution of 3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzaldehyde (100 mg, 0.213 mmol) in THF (2.1 mL) at 0° C. was added methylmagnesium bromide (1 M in THF, 213  $\mu$ L, 0.638 mmol). The reaction mixture was warmed up to r.t. and stirred for 1 hr, and then quenched with sat. ammonium chloride and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. To the residue was added DCM (2 mL) and manganese dioxide (185 mg, 2.125 mmol). After stirring at 60° C. for 1 hr, the mixture was filtered through a plug of Celite and concentrated. The residue was purified by Biotage Isolera™ (flash purification system with dichloromethane/methanol at a ratio from 2 to 10%) to provide the desired product as a white solid. LCMS calculated for  $C_{23}H_{27}F_2N_6O_2Si$  [M+H]<sup>+</sup> m/z: 485.2; Found: 485.2.

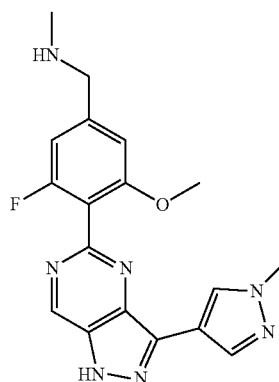
Step 2. 1-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylethanamine

[0731] A solution of 1-(3,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)ethan-1-one (25 mg, 0.052 mmol), methanamine (0.129 mL, 0.258 mmol) in toluene (1 mL) was stirred at 80° C. overnight. The reaction mixture was then concentrated and redissolved in methanol (1 mL). Sodium borohydride (5.86 mg, 0.155 mmol) was then added, and the mixture was stirred at r.t. for 30 mins. 4N HCl in dioxane was then added and stirring was continued at 80° C. for 30 mins. The mixture was then diluted with methanol and purified directly on prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to provide the desired product. LC-MS calculated for  $C_{18}H_{18}F_2N_7$  [M+H]<sup>+</sup> m/z: 370.2, found 370.2.

Example 86

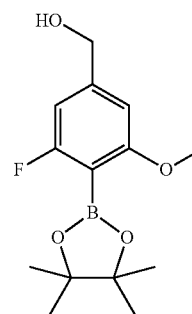
1-(3-Fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0732]



Step 1. (3-Fluoro-5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol

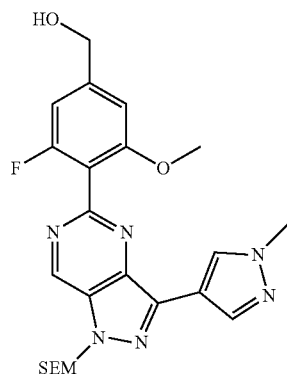
[0733]



[0734] To a solution of (3-fluoro-5-methoxyphenyl)methanol (575 mg, 3.68 mmol) in THF (18 mL) at -78° C. was added n-BuLi (1.6 M in hexanes, 4.8 mL, 7.73 mmol) and the reaction mixture was stirred at -78° C. for 1 hr. Then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1581  $\mu$ L, 7.73 mmol) was added dropwise and stirring was continued at -78° C. for 0.5 hrs, then the mixture was warmed to r.t. by removal from the cold bath. When room temperature was reached, the reaction mixture was then quenched with 1N HCl until acidic and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The crude residue was used in the next step without further purification.

Step 2. (3-Fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)methanol

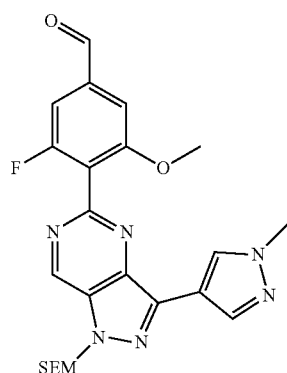
[0735]



[0736] To a mixture of 5-chloro-3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (500 mg, 1.370 mmol), (3-fluoro-5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (1160 mg, 4.11 mmol), XPhos Pd G2 (108 mg, 0.137 mmol) and potassium phosphate (582 mg, 2.74 mmol) were added 1,4-dioxane (3.6 mL) and water (900  $\mu$ L). The reaction flask was evacuated, back filled with nitrogen, and the reaction mixture was then stirred at 95° C. for 2 hours. The mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and purified by Biotage Isolera™ (flash purification system with dichloromethane/methanol at a ratio from 2 to 10%) to provide the desired product as an oil. LCMS calculated for  $C_{23}H_{30}FN_6O_3Si$  [M+H]<sup>+</sup> m/z: 485.2; Found: 485.2.

Step 3. 3-Fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzaldehyde

[0737]



[0738] To a solution of (3-fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)methanol (309 mg, 0.638 mmol) in DCM (6.4 mL) was added manganese dioxide (554 mg, 6.38 mmol) and the reaction

mixture was heated to 60° C. for 1 h, then cooled, filtered through a plug of Celite and concentrated. The residue was purified by Biotage Isolera™ (flash purification system with dichloromethane/methanol at a ratio from 2 to 10%) to provide the desired product as an oil. LCMS calculated for  $C_{23}H_{28}FN_6O_3Si$  [M+H]<sup>+</sup> m/z: 483.2; Found: 483.2.

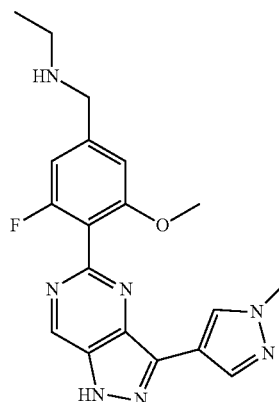
Step 4. 1-(3-Fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0739] To a solution of 3-fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzaldehyde (25 mg, 0.052 mmol) and methanamine (2 M in THF, 0.130 mL, 0.259 mmol) in toluene (1 mL) was added acetic acid (8.90  $\mu$ L, 0.155 mmol) and the reaction mixture was heated to 80° C. overnight. The mixture was then cooled down to r.t. and concentrated. The residue was redissolved in MeOH (1 mL) and sodium borohydride (1.960 mg, 0.052 mmol) was added. After 30 mins, 4 N HCl in dioxane was added (1 mL) and the mixture heated to 80° C. for 30 mins, then diluted with methanol and purified directly on prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to provide the desired product. LC-MS calculated for  $C_{18}H_{19}FN_7O$  [M+H]<sup>+</sup> m/z: 368.2, found 368.2.

#### Example 87

N-(3-Fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzyl)ethanamine

[0740]

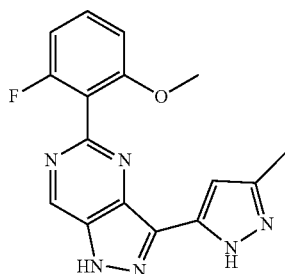


[0741] This compound was prepared using procedures analogous to those for example 86, with ethyl amine (88% in water) replacing methylamine. LCMS calculated for  $C_{19}H_{21}FN_7O$  [M+H]<sup>+</sup> m/z: 382.2; Found: 382.2.

## Example 88

5-(2-Fluoro-6-methoxyphenyl)-3-(3-methyl-1H-pyrazol-5-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0742]

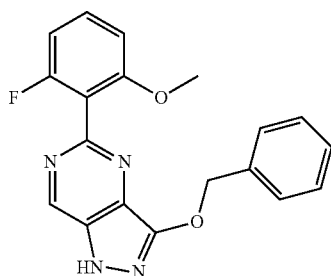


[0743] This compound was prepared using procedures analogous to those for Example 12, with 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing phenylboronic acid as starting material. LCMS calculated for  $C_{16}H_{14}FN_6O$   $[M+H]^+$   $m/z$ : 325.2; Found: 325.2.

## Example 89

3-(Benzyloxy)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0744]

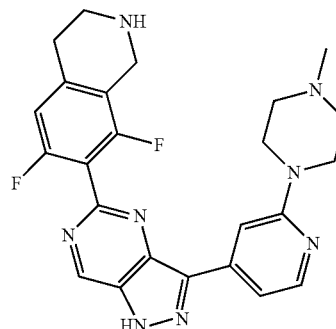


[0745] To a mixture of 5-(2-fluoro-6-methoxyphenyl)-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (30 mg, 0.060 mmol, Example 12, Step 5), benzyl alcohol (62.3  $\mu$ L, 0.600 mmol), cesium carbonate (58.6 mg, 0.180 mmol) and t-BuBrettPhos Pd G3 (4 mg) was added 1,4-dioxane (700  $\mu$ L). The reaction flask was evacuated, back filled with nitrogen, and the reaction mixture was then stirred at 100° C. overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. To the residue were added methanol (1 mL) and HCl (4M in dioxane, 1 mL). After stirring at 80° C. for 1 hr, the mixture was diluted with methanol and purified directly on prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to provide the desired product. LC-MS calculated for  $C_{19}H_{16}FN_4O_2$   $[M+H]^+$   $m/z$ : 351.2, found 351.2.

## Example 90

6,8-Difluoro-7-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

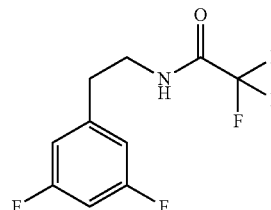
[0746]



## Step 1.

N-(3,5-Difluorophenethyl)-2,2,2-trifluoroacetamide

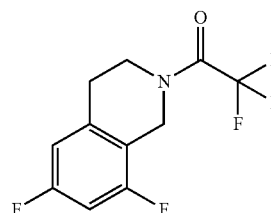
[0747]



[0748] To a solution of 2-(3,5-difluorophenyl)ethan-1-amine (AURUM Pharmatech, 5.023 g, 32.0 mmol) in  $CH_2Cl_2$  (100.0 mL) was added triethylamine (9.90 mL, 71.0 mmol). The mixture was cooled to -15° C. Then trifluoroacetic anhydride (6.15 mL, 43.6 mmol) was added dropwise. The mixture was allowed to warm to room temperature. After stirring at room temperature for 30 mins, the reaction mixture was poured into ice and extracted with  $CH_2Cl_2$ . The organic layer was dried over anhydrous  $Na_2SO_4$ , filtered and concentrated to give the crude product as a pale yellow solid that was used directly in the next step without further purification (8.96 g). LCMS calculated for  $C_{10}H_9F_5NO$   $(M+H)^+$   $m/z$ : 254.1; found 254.2.

Step 2. 1-(6,8-Difluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone

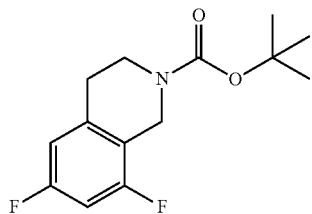
[0749]



**[0750]** To a solution of N-(3,5-difluorophenethyl)-2,2,2-trifluoroacetamide (6.29 g, 24.84 mmol) in acetic acid (80.0 ml) at 0° C. was added sulfuric acid (50.0 ml) slowly. Then paraformaldehyde (1.967 g, 65.5 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 5 h. The mixture was poured into ice, and extracted with EtOAc. The organic layer was washed with 2 M K<sub>2</sub>CO<sub>3</sub>(aq), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (3.867 g, 59%). LCMS calculated for C<sub>11</sub>H<sub>9</sub>F<sub>5</sub>NO (M+H)<sup>+</sup> m/z=266.1; found 266.1.

Step 3. tert-Butyl 6,8-difluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate

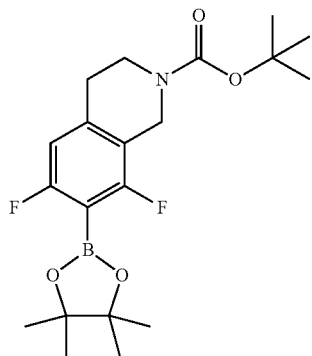
**[0751]**



**[0752]** To a solution of 1-(6,8-difluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethan-1-one (3.867 g, 14.58 mmol) in MeOH (70.0 ml) was added potassium carbonate (6.56 g, 47.5 mmol) followed by H<sub>2</sub>O (25.0 ml). The mixture was stirred at 50° C. for 2 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 ml). Boc-anhydride (3.56 g, 16.31 mmol) was added followed by DMAP (548.6 mg, 4.49 mmol). The reaction mixture was stirred at room temperature for 30 mins and MeOH (50 ml) was added. The reaction was concentrated. The residue was purified on silica gel (120 g, 0-50% EtOAc in hexanes) to give the desired product as a colorless oil (3.77 g, 96%). LCMS calculated for C<sub>10</sub>H<sub>10</sub>F<sub>2</sub>NO<sub>2</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup>: m/z=214.1; found: 214.1.

Step 4. tert-Butyl 6,8-difluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

**[0753]**

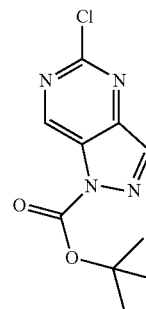


**[0754]** To a solution of tert-butyl 6,8-difluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (3.76 g, 13.96 mmol) in THF (100.0 ml) under N<sub>2</sub> at -78° C. was added a solution of LDA (1.0 M in THF/hexanes) (36.0 ml, 36.0 mmol) dropwise via syringe over a period of 40 mins. The reaction

was allowed to warm to -60° C. and stirred for 60 mins. The reaction was then cooled back to -78° C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.52 ml, 51.5 mmol) was added slowly over a period of 20 min. After stirring at -78° C. for 20 min, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with sat. NaHCO<sub>3</sub>, and extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (120 g, 0-50% EtOAc in hexanes) to give the desired product as a white solid (4.11 g, 75%). LCMS calculated for C<sub>16</sub>H<sub>21</sub>BF<sub>2</sub>NO<sub>4</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup>: m/z=340.2; found: 340.1.

Step 5. tert-Butyl 5-chloro-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

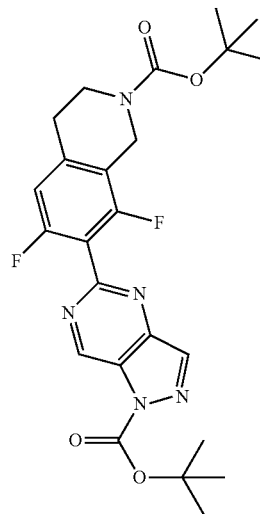
**[0755]**



**[0756]** To a solution of 5-chloro-1H-pyrazolo[4,3-d]pyrimidine (3.034 g, 19.63 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100.0 ml) was added boc-anhydride (7.15 ml, 30.8 mmol) followed by DMAP (728.8 mg, 5.97 mmol). The reaction was stirred at room temperature for 16 h. MeOH (50 ml) was added. The mixture was stirred at room temperature for 2 h, and then concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (3.78 g, 76%). LCMS calculated for C<sub>10</sub>H<sub>12</sub>ClN<sub>4</sub>O<sub>2</sub> (M+H)<sup>+</sup> m/z=255.1; found 255.1.

Step 6. tert-Butyl 7-(1-(tert-butoxycarbonyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate

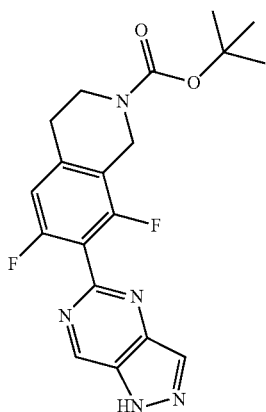
**[0757]**



**[0758]** To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (1388 mg, 5.45 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 807.5 mg, 1.026 mmol) and cesium carbonate (4851 mg, 14.89 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 6,8-difluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.054 g, 5.20 mmol) in 1,4-dioxane (15.00 ml) was added via syringe, followed by water (6.00 ml). The reaction was stirred at 60° C. for 2 h. The separated organic layer was concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a yellow foamy solid (2.410 g, 95%). LCMS calculated for  $C_{24}H_{27}F_2N_5NaO_4$  (M+Na)<sup>+</sup> m/z=510.2; found 510.2.

Step 7. tert-Butyl 6,8-difluoro-7-(1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

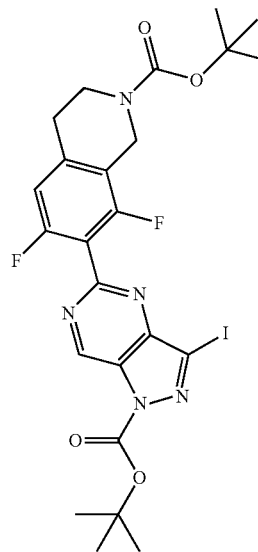
**[0759]**



**[0760]** To a mixture of tert-butyl 7-(1-(tert-butoxycarbonyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (2410 mg, 4.94 mmol), potassium carbonate (4755 mg, 34.4 mmol) was added 1,4-dioxane (25.0 ml) followed by water (25.0 ml). The mixture was stirred at 80° C. for 10 h. After cooling to room temperature, the mixture was diluted with  $CH_2Cl_2$ , and washed with brine. The organic layer was dried over anhydrous  $Na_2SO_4$ , filtered and concentrated to give the crude product as a yellow solid that was used directly in the next step without further purification. LCMS calculated for  $C_{19}H_{20}F_2N_5O_2$  (M+H)<sup>+</sup> m/z=388.2; found 388.1.

Step 8. tert-Butyl 7-(1-(tert-butoxycarbonyl)-3-iodo-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate

**[0761]**



**[0762]** To a solution of tert-butyl 6,8-difluoro-7-(1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (step 7) in DMF (30.0 ml) was added N-iodosuccinimide (1342 mg, 5.96 mmol). The mixture was stirred at 80° C. for 90 mins, and then cooled to room temperature. Boc-anhydride (1753 mg, 8.03 mmol) was added followed by DMAP (243.4 mg, 1.992 mmol). The reaction was stirred at room temperature for 20 mins. The mixture was diluted with  $CH_2Cl_2$ , and washed with sat.  $NaHCO_3$  (aq). The organic layer was dried over anhydrous  $Na_2SO_4$ , filtered and concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white foamy solid (2041 mg, 67% over 2 steps). LCMS calculated for  $C_{24}H_{27}F_2IN_5O_4$  (M+H)<sup>+</sup> m/z=614.1; found 614.1.

Step 9. 6,8-Difluoro-7-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

**[0763]** To a screw-cap vial equipped with a magnetic stir bar was added 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (22.5 mg, 0.074 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 6.0 mg, 7.63  $\mu$ mol) and cesium carbonate (56.7 mg, 0.174 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 7-(1-(tert-butoxycarbonyl)-3-iodo-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (30.0 mg, 0.049 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added  $CH_2Cl_2$  (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at

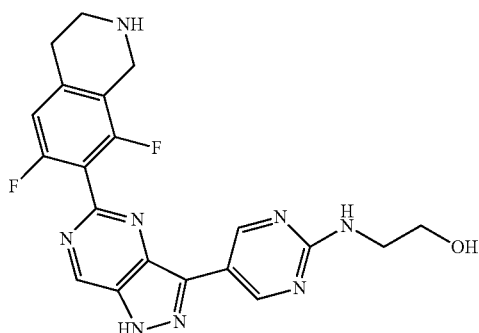


room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for  $C_{24}H_{25}F_2N_8$  (M+H)<sup>+</sup>: m/z=463.2; found: 463.3.

## Example 91

2-(5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyrimidin-2-ylamino)ethanol

[0764]

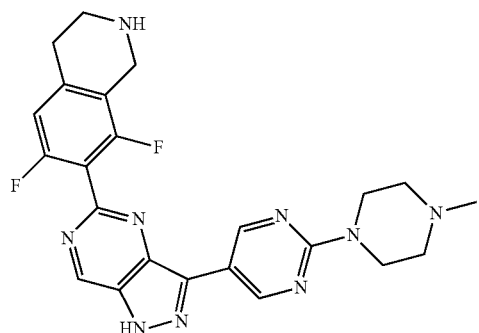


[0765] This compound was prepared according to the procedure described in Example 90 (step 9), using 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-ylamino)ethanol instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{20}H_{19}F_2N_8O$  (M+H)<sup>+</sup>: m/z=425.2; found: 425.2.

## Example 92

6,8-Difluoro-7-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0766]



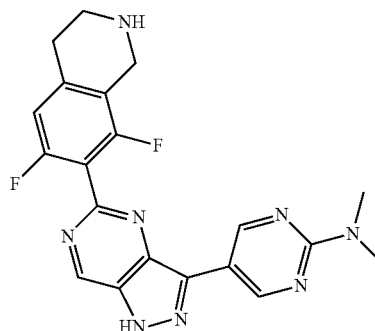
[0767] This compound was prepared according to the procedure described in Example 90 (step 9), using 2-(4-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{24}H_{25}F_2N_8$  (M+H)<sup>+</sup>: m/z=463.2; found: 463.3.

piperazine as the starting material. LCMS calculated for  $C_{23}H_{24}F_2N_9$  (M+H)<sup>+</sup>: m/z=464.2; found: 464.3.

## Example 93

5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N,N-dimethylpyrimidin-2-amine

[0768]

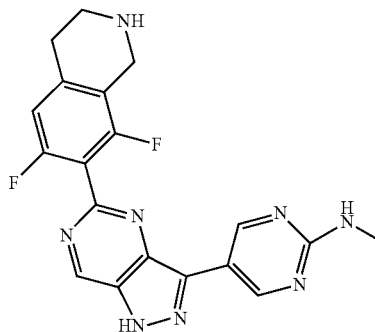


[0769] This compound was prepared according to the procedure described in Example 90 (step 9), using N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{20}H_{19}F_2N_8$  (M+H)<sup>+</sup>: m/z=409.2; found: 409.3.

## Example 94

5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N-methylpyrimidin-2-amine

[0770]

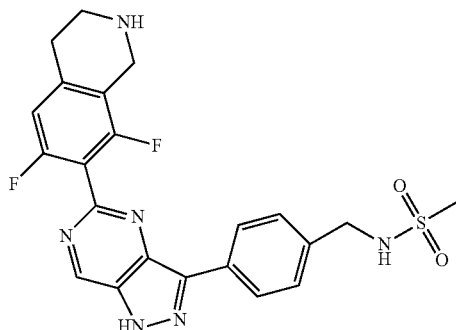


[0771] This compound was prepared according to the procedure described in Example 90 (step 9), using N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{19}H_{17}F_2N_8$  (M+H)<sup>+</sup>: m/z=395.2; found: 395.2.

## Example 95

N-(4-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzyl) methanesulfonamide

[0772]

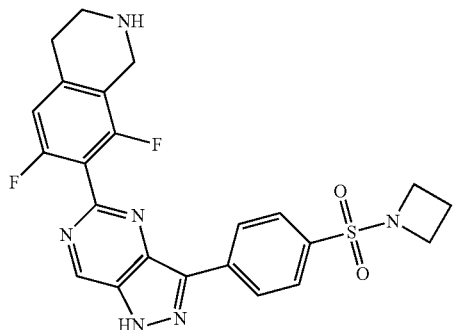


[0773] This compound was prepared according to the procedure described in Example 90 (step 9), using 4-(methylsulfonamidomethyl)phenylboronic acid instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{22}H_{21}F_2N_6O_2S$  ( $M+H$ )<sup>+</sup>:  $m/z=471.1$ ; found: 471.2.

## Example 96

7-(3-(4-(Azetidin-1-ylsulfonyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-1,2,3,4-tetrahydroisoquinoline

[0774]

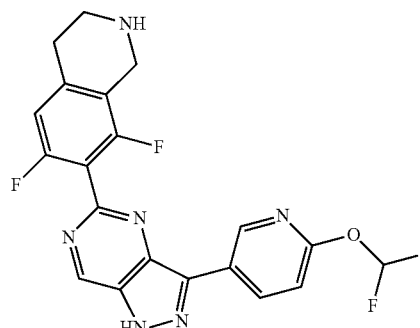


[0775] This compound was prepared according to the procedure described in Example 90 (step 9), using 4-(azetidin-1-ylsulfonyl)phenylboronic acid instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{23}H_{21}F_2N_6O_2S$  ( $M+H$ )<sup>+</sup>:  $m/z=483.1$ ; found: 483.2.

## Example 97

7-(3-(6-(Difluoromethoxy)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-1,2,3,4-tetrahydroisoquinoline

[0776]

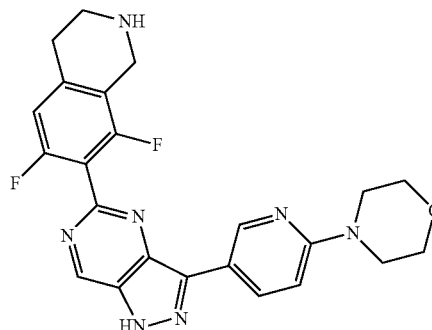


[0777] This compound was prepared according to the procedure described in Example 90 (step 9), using 2-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{20}H_{15}F_4N_6O$  ( $M+H$ )<sup>+</sup>:  $m/z=431.1$ ; found: 431.2.

## Example 98

4-(5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)morpholine

[0778]

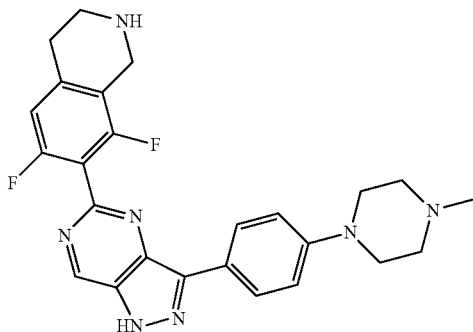


[0779] This compound was prepared according to the procedure described in Example 90 (step 9), using 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{23}H_{22}F_2N_7O$  ( $M+H$ )<sup>+</sup>:  $m/z=450.2$ ; found: 450.2. <sup>1</sup>H NMR (TFA salt, 500 MHz, DMSO)  $\delta$  9.50 (s, 1H), 9.30 (br, 2H), 9.17 (d,  $J=2.2$  Hz, 1H), 8.44 (dd,  $J=9.0, 2.2$  Hz, 1H), 7.25 (d,  $J=9.9$  Hz, 1H), 7.04 (d,  $J=9.0$  Hz, 1H), 4.35 (s, 2H), 3.76-3.66 (m, 4H), 3.57-3.49 (m, 4H), 3.44 (m, 2H), 3.11 (t,  $J=6.1$  Hz, 2H).

## Example 99

6,8-Difluoro-7-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0780]

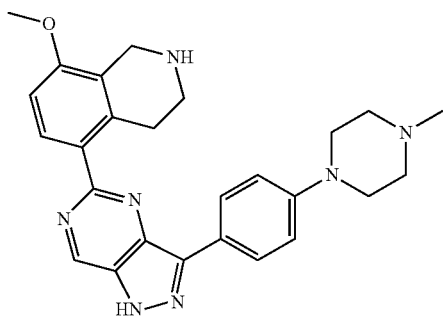


[0781] This compound was prepared according to the procedure described in Example 90 (step 9), using 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) piperazine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{25}H_{26}F_2N_7$  ( $M+H$ )<sup>+</sup>:  $m/z=462.2$ ; found: 462.3. <sup>1</sup>H NMR (TFA salt, 600 MHz, DMSO)  $\delta$  10.12 (br, 1H), 9.48 (s, 1H), 9.42 (br, 2H), 8.30 (d,  $J=8.9$  Hz, 2H), 7.25 (d,  $J=9.8$  Hz, 1H), 7.16 (d,  $J=8.9$  Hz, 2H), 4.34 (s, 2H), 3.95 (m, 2H), 3.53 (m, 2H), 3.45 (m, 2H), 3.17 (m, 2H), 3.11 (t,  $J=6.1$  Hz, 2H), 3.06 (m, 2H), 2.86 (s, 3H).

## Example 100

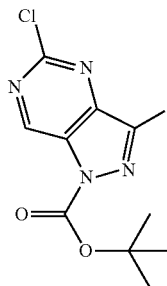
8-Methoxy-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0782]



Step 1. tert-Butyl 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

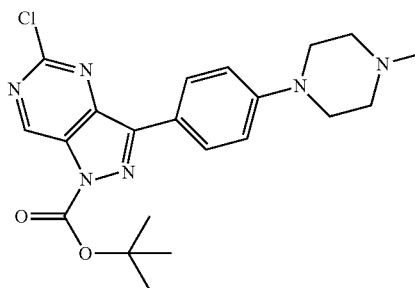
[0783]



[0784] To a solution of 5-chloro-1H-pyrazolo[4,3-d]pyrimidine (4.97 g, 32.2 mmol) in DMF (120.0 ml) was added N-iodosuccinimide (7.967 g, 35.4 mmol). The mixture was stirred at 80° C. for 1 h. After cooling to room temperature, boc-anhydride (11.32 ml, 48.8 mmol) was added followed by DMAP (1.296 g, 10.61 mmol). The reaction was stirred at room temperature for 20 mins. The mixture was diluted with Et<sub>2</sub>O and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (4.435 g, 49%). LCMS calculated for  $C_{10}H_{11}ClIN_4O_2$  ( $M+H$ )<sup>+</sup>  $m/z=381.0$ ; found 381.0.

Step 2. tert-Butyl 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

[0785]

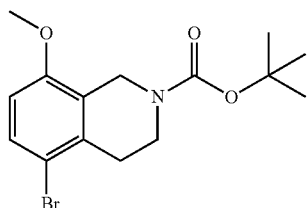


[0786] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (700.0 mg, 1.839 mmol), (4-(4-methylpiperazin-1-yl)phenyl)boronic acid (509.0 mg, 2.313 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (300.1 mg, 0.367 mmol) and cesium carbonate (1991 mg, 6.11 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (10.0 ml) was added, followed by water (3.0 ml). The reaction mixture was stirred at 50° C. for 16 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>,

filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes then 10% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to give the desired product as a brown solid (752.2 mg, 95%). LCMS calculated for  $\text{C}_{21}\text{H}_{26}\text{ClN}_6\text{O}_2$  ( $\text{M}+\text{H}$ )<sup>+</sup>  $m/z=429.2$ ; found 429.2.

Step 3. tert-Butyl 5-bromo-8-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate

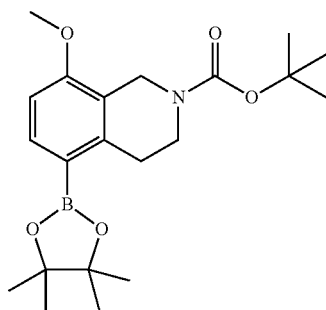
[0787]



[0788] To a solution of 5-bromo-8-methoxy-1,2,3,4-tetrahydroisoquinoline, HCl salt (857.7 mg, 3.08 mmol) in  $\text{CH}_2\text{Cl}_2$  (10.0 ml) was added N,N-diisopropylethylamine (1.209 ml, 6.92 mmol). The mixture was stirred at room temperature for 10 mins, and then a solution of boc-anhydride (828.2 mg, 3.79 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 ml) was added. After stirring at room temperature for 30 mins, the reaction was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as an oil (1.048 g, 99%). LCMS calculated for  $\text{C}_{11}\text{H}_{13}\text{BrNO}_3$  ( $\text{M}+\text{H}-\text{C}_4\text{H}_8$ )<sup>+</sup>:  $m/z=286.0$ ; found: 286.0.

Step 4. tert-Butyl 8-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[0789]



[0790] To a screw-cap vial equipped with a magnetic stir bar was added 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (1174 mg, 4.62 mmol), potassium acetate (1214 mg, 12.37 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (500.3 mg, 0.613 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 5-bromo-8-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (1048 mg, 3.06 mmol) in 1,4-dioxane (15.0 mL) was added via syringe. The mixture was stirred at 100° C. for 16 h. After cooling to

room temperature, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and filtered. The filtrate was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product (959.8 mg, 81%). LCMS calculated for  $\text{C}_{17}\text{H}_{25}\text{BNO}_5$  ( $\text{M}+\text{H}-\text{C}_4\text{H}_8$ )<sup>+</sup>:  $m/z=334.2$ ; found: 334.1.

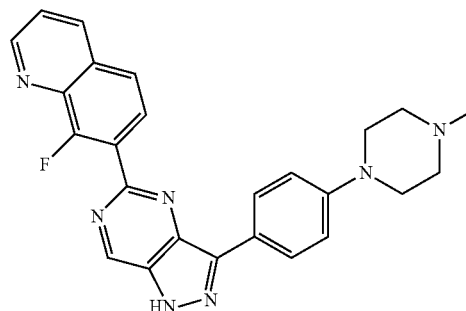
Step 5. 8-Methoxy-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0791] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (39.7 mg, 0.093 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)] palladium(II) (XPhos Pd G2, 9.0 mg, 0.011 mmol) and cesium carbonate (81.5 mg, 0.250 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 8-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (29.7 mg, 0.076 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0  $\mu\text{l}$ ). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added  $\text{CH}_2\text{Cl}_2$  (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for  $\text{C}_{26}\text{H}_{30}\text{N}_7\text{O}$  ( $\text{M}+\text{H}$ )<sup>+</sup>:  $m/z=456.3$ ; found: 456.2.

Example 101

8-Fluoro-7-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)quinoline

[0792]

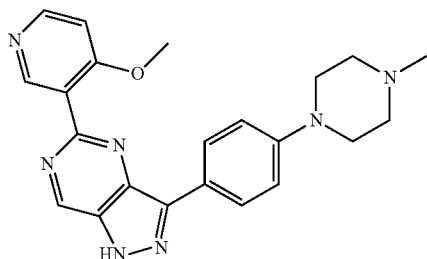


[0793] This compound was prepared according to the procedure described in Example 100 (step 5), using 8-fluoroquinolin-7-ylboronic acid instead of tert-butyl 8-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate as the starting material. LCMS calculated for  $\text{C}_{25}\text{H}_{23}\text{FN}_7$  ( $\text{M}+\text{H}$ )<sup>+</sup>:  $m/z=440.2$ ; found: 440.2.

## Example 102

5-(4-Methoxypyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0794]

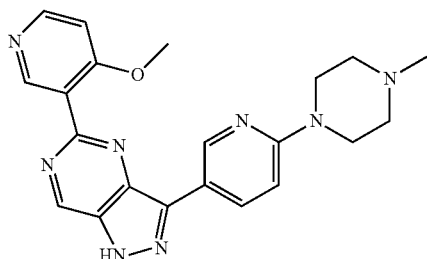


[0795] This compound was prepared according to the procedure described in Example 100 (step 5), using 4-methoxypyridin-3-ylboronic acid instead of tert-butyl 8-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate as the starting material. LCMS calculated for  $C_{22}H_{24}N_7O$  (M+H)<sup>+</sup>: m/z=402.2; found: 402.2.

## Example 103

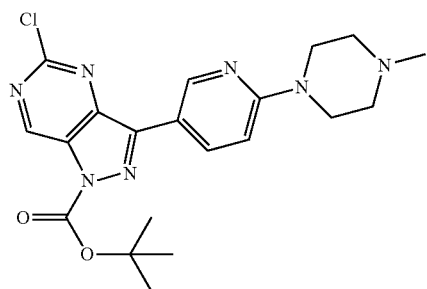
5-(4-Methoxypyridin-3-yl)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0796]



Step 1. tert-Butyl 5-chloro-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

[0797]



[0798] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (900.0 mg, 2.365 mmol), 1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (732.2 mg, 2.415 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complexed with dichloromethane (1:1) (386.1 mg, 0.473 mmol) and cesium carbonate (2621 mg, 8.04 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (10.0 ml) was added, followed by water (3.0 ml). The reaction was stirred at 50° C. for 16 h. After cooling to room temperature, the mixture was diluted with  $CH_2Cl_2$ , and washed with brine. The organic layer was dried over anhydrous  $Na_2SO_4$ , filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes then 10% MeOH in  $CH_2Cl_2$ ) to give the desired product as a yellow solid (746.2 mg, 73%). LCMS calculated for  $C_{20}H_{25}ClN_7O_2$  (M+H)<sup>+</sup> m/z=430.2; found 430.2.

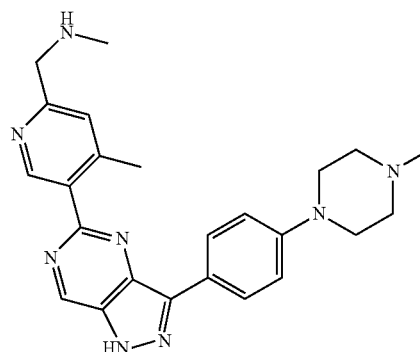
Step 2. 5-(4-Methoxypyridin-3-yl)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine

[0799] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (24.7 mg, 0.057 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 7.0 mg, 8.90  $\mu$ mol) and cesium carbonate (66.2 mg, 0.203 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of (4-methoxypyridin-3-yl)boronic acid (23.6 mg, 0.154 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added  $CH_2Cl_2$  (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for  $C_{21}H_{23}N_8O$  (M+H)<sup>+</sup>: m/z=403.2; found: 403.2.

## Example 104

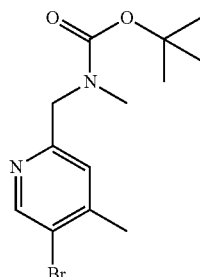
N-Methyl-1-(4-methyl-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-2-yl)methanamine

[0800]



Step 1. tert-Butyl (5-bromo-4-methylpyridin-2-yl)methyl(methyl)carbamate

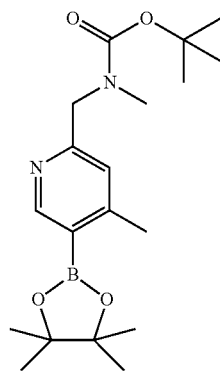
[0801]



[0802] To a solution of 5-bromo-4-methylpicolinaldehyde (1.044 g, 5.22 mmol) in MeOH (20.0 ml) was added 2.0 M methylamine in MeOH (8.0 ml, 16.00 mmol) followed by sodium cyanoborohydride (1.313 g, 20.89 mmol) and acetic acid (1.00 ml, 17.47 mmol). After stirring at room temperature for 90 mins, the reaction was quenched with HCl (6.0 N in water) (25.0 ml, 150 mmol). The mixture was stirred at room temperature for 30 mins, and treated with NaOH (4 N in water) until pH reached 10. The mixture was extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), and treated with Boc-anhydride (1.198 g, 5.49 mmol). After stirring at room temperature for 30 mins, the reaction was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a yellow oil (1.101 g, 67%). LCMS calculated for C<sub>13</sub>H<sub>20</sub>BrN<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> m/z=315.1; found 315.0.

Step 2. tert-Butyl methyl((4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methyl)carbamate

[0803]



[0804] To a screw-cap vial equipped with a magnetic stir bar was added 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (1.216 g, 4.79 mmol), potassium acetate (1.143 g, 11.65 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (450.3 mg, 0.551 mmol). The vial was

sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl ((5-bromo-4-methylpyridin-2-yl)methyl(methyl)carbamate (1.101 g, 3.49 mmol) in 1,4-dioxane (17.0 ml) was added via syringe. The mixture was stirred at 80° C. for 16 h. After cooling to room temperature, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and filtered. The filtrate was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes then 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give the desired product (461.0 mg, 36%).

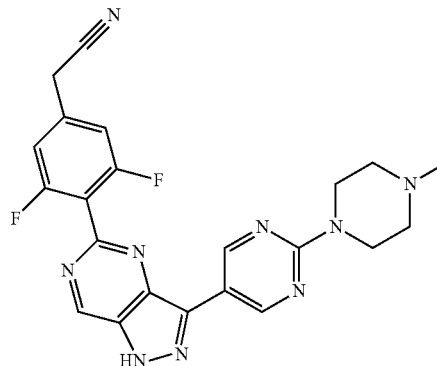
Step 3. N-Methyl-1-(4-methyl-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-2-yl)methanamine

[0805] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (47.0 mg, 0.110 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)] palladium(II) (XPhos Pd G2, 13.0 mg, 0.017 mmol) and cesium carbonate (115.5 mg, 0.354 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl methyl((4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methyl)carbamate (59.8 mg, 0.165 mmol) in 1,4-dioxane (3.00 ml) was added via syringe, followed by water (300.0 μl). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>24</sub>H<sub>29</sub>N<sub>8</sub> (M+H)<sup>+</sup>: m/z=429.3; found: 429.3.

Example 105

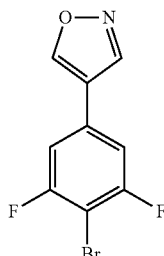
2-(3,5-Difluoro-4-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)acetonitrile

[0806]



## Step 1. 4-(4-Bromo-3,5-difluorophenyl)isoxazole

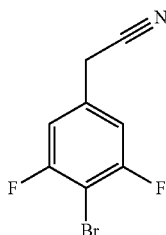
[0807]



[0808] To a screw-cap vial equipped with a magnetic stir bar was added 2-bromo-1,3-difluoro-5-iodobenzene (1360.8 mg, 4.27 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (828.0 mg, 4.25 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (727.0 mg, 0.890 mmol) and cesium carbonate (2843 mg, 8.73 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (12.0 ml) was added via syringe followed by water (2.0 ml). The reaction was heated to 50° C. for 16 h. After cooling to room temperature, the organic layer was separated and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a pale yellow solid (502.9 mg, 46%).

## Step 2. 2-(4-Bromo-3,5-difluorophenyl)acetonitrile

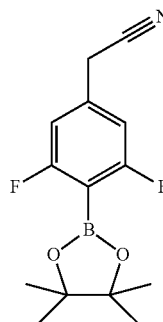
[0809]



[0810] To a mixture of 4-(4-bromo-3,5-difluorophenyl)isoxazole (489.4 mg, 1.882 mmol) and potassium fluoride (584.8 mg, 10.07 mmol) was added DMF (5.0 ml) followed by water (5.0 ml). The reaction was heated to 90° C. for 3 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as an off-white solid (363.4 mg, 83%).

## Step 3. 2-(3,5-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile

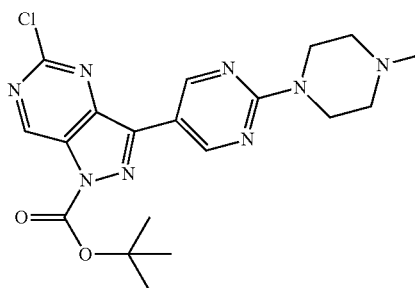
[0811]



[0812] To a screw-cap vial equipped with a magnetic stir bar was added 4,4,5,5,4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (607.8 mg, 2.393 mmol), potassium acetate (643.7 mg, 6.56 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complexed with dichloromethane (1:1) (256.1 mg, 0.314 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of 2-(4-bromo-3,5-difluorophenyl)acetonitrile (363.4 mg, 1.566 mmol) in 1,4-dioxane (10.0 mL) was added via syringe. The mixture was stirred at 100° C. for 16 h. After cooling to room temperature, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and filtered. The filtrate was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes then 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give the desired product (229.4 mg, 53%). LCMS calculated for C<sub>14</sub>H<sub>17</sub>BF<sub>2</sub>NO<sub>2</sub> (M+H)<sup>+</sup>: m/z=280.1; found: 280.0.

## Step 4. tert-Butyl 5-chloro-3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

[0813]



[0814] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (1026.0 mg, 2.70 mmol), 2-(4-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (816.5 mg, 2.68 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (440.2 mg, 0.539 mmol) and cesium carbonate (2693 mg, 8.27 mmol). The

vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (12.0 ml) was added, followed by water (4.0 ml). The reaction was stirred at 50° C. for 16 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes then 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give the desired product as a yellow solid (877.3 mg, 76%). LCMS calculated for C<sub>19</sub>H<sub>24</sub>ClN<sub>8</sub>O<sub>2</sub> (M+H)<sup>+</sup> m/z=431.2; found 431.1.

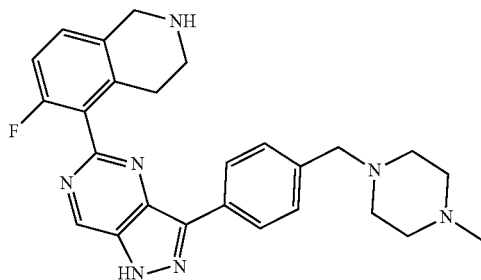
Step 5. 2-(3,5-Difluoro-4-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)acetonitrile

[0815] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (33.3 mg, 0.077 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (9.0 mg, 0.011 mmol) and cesium carbonate (83.0 mg, 0.255 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of 2-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile (34.6 mg, 0.124 mmol) in 1,4-dioxane (2.0 ml) was added via syringe, followed by water (200.0 µl). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>22</sub>H<sub>20</sub>F<sub>2</sub>N<sub>9</sub> (M+H)<sup>+</sup>: m/z=448.2; found: 448.2.

#### Example 106

6-Fluoro-5-(3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

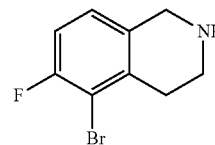
[0816]



Step 1.

5-Bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline

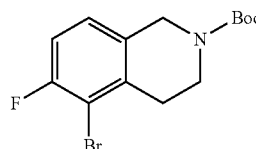
[0817]



[0818] To a solution of 5-bromo-6-fluoroisoquinoline (1.002 g, 4.433 mmol) in acetic acid (20.0 mL) at room temperature was added sodium tetrahydroborate (592.0 mg, 15.65 mmol) portion wise. The mixture was stirred at room temperature for 16 h, and then concentrated. The residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 2 M Na<sub>2</sub>CO<sub>3</sub> (aq). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a yellow oil that was used directly in the next step without further purification. LCMS calculated for C<sub>9</sub>H<sub>10</sub>BrFN (M+H)<sup>+</sup> m/z=230.0; found 230.1.

Step 2. tert-Butyl 5-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate

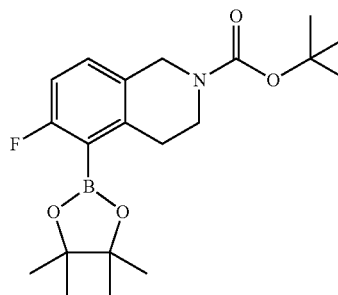
[0819]



[0820] To a solution of 5-bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline (1.020 g, 4.433 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12.0 mL) was added di-tert-butyl dicarbonate (1.617 g, 7.409 mmol). The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (1.119 g, 76% over two steps). LCMS calculated for C<sub>14</sub>H<sub>17</sub>BrFNNaO<sub>2</sub> (M+Na)<sup>+</sup> m/z=352.0; found 352.0.

Step 3. tert-Butyl 6-fluoro-5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[0821]

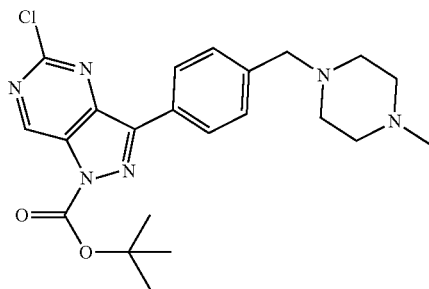




**[0822]** To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.119 g, 3.389 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (1.358 g, 5.348 mmol), potassium acetate (1.101 g, 11.22 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (298.6 mg, 0.366 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (15.0 mL) was added via syringe. The mixture was heated at 100° C. for 16 h. After cooling to room temperature, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and filtered. The filtrate was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a pale yellow oil (1001 mg, 78%). LCMS calculated for C<sub>26</sub>H<sub>29</sub>BFNNaO<sub>4</sub> (M+Na)<sup>+</sup> m/z=400.2; found 400.2.

Step 4. tert-Butyl 5-chloro-3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

**[0823]**



**[0824]** To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (1126.0 mg, 2.96 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine (949.2 mg, 3.00 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (450.5 mg, 0.552 mmol) and cesium carbonate (2892.3 mg, 8.88 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (12.0 ml) was added via syringe, followed by water (4.0 ml). The reaction was stirred at 50° C. for 16 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes then 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give the desired product as a yellow solid (927.3 mg, 71%). LCMS calculated for C<sub>22</sub>H<sub>28</sub>ClN<sub>6</sub>O<sub>2</sub> (M+H)<sup>+</sup> m/z=443.2; found 443.2.

Step 5. 6-Fluoro-5-(3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

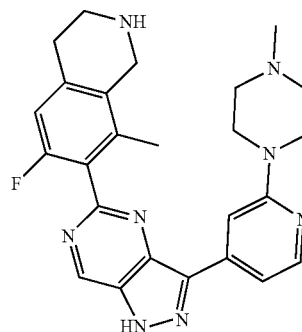
**[0825]** To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(4-((4-methylpiperazin-

1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (26.5 mg, 0.060 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 7.0 mg, 8.90 μmol) and cesium carbonate (68.0 mg, 0.209 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (22.6 mg, 0.060 mmol) in 1,4-dioxane (2.0 ml) was added via syringe, followed by water (200.0 μl). The reaction was heated to 50° C. for 16 h. The reaction mixture was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The resulting mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>26</sub>H<sub>29</sub>FN<sub>7</sub> (M+H)<sup>+</sup> m/z=458.2; found: 458.3.

Example 107

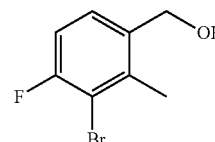
6-Fluoro-8-methyl-7-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

**[0826]**



Step 1.  
(3-Bromo-4-fluoro-2-methylphenyl)methanol

**[0827]**

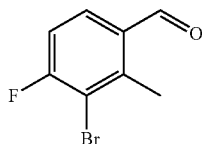


**[0828]** To a solution of ethyl 3-bromo-4-fluoro-2-methylbenzoate (Enamine, 6.535 g, 25.03 mmol) in THF (60.0 ml) was added BH<sub>3</sub>\*THF (1.0 M in THF) (125 ml, 125 mmol). The mixture was stirred at 65° C. for 16 h. The reaction was cooled to room temperature, and MeOH (100.0 ml) was added. After stirring at room temperature for 2 h, the mixture was cooled to 0° C. HCl (4.0 M in water) (100 ml, 400 mmol) was added. The mixture was extracted with Et<sub>2</sub>O.

The separated organic layer was washed with sat.  $\text{NaHCO}_3$ , dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give the crude product as a white solid (5.35 g, 98%).

Step 2. 3-Bromo-4-fluoro-2-methylbenzaldehyde

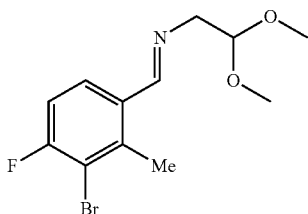
[0829]



[0830] To a solution of (3-bromo-4-fluoro-2-methylphenyl)methanol (5.35 g, 24.42 mmol) in  $\text{CH}_2\text{Cl}_2$  (120.0 ml) was added manganese dioxide (activated) (36.6 g, 379 mmol). The mixture was stirred at room temperature for 16 h. The mixture was filtered through a pad of Celite. The Celite pad was further rinsed with  $\text{CH}_2\text{Cl}_2$ . The combined filtrate was concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a yellow solid (4.427 g, 84%).

Step 3. N-(3-Bromo-4-fluoro-2-methylbenzylidene)-2,2-dimethoxyethanamine

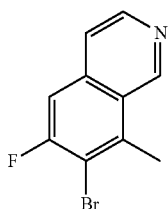
[0831]



[0832] To a solution of 3-bromo-4-fluoro-2-methylbenzaldehyde (6.086 g, 28.0 mmol) in toluene (100.0 ml) was added 2,2-dimethoxyethan-1-amine (3.13 mL, 28.6 mmol). The mixture was refluxed for 16 h with a Dean-Stark trap. After cooling to room temperature, the mixture was concentrated to give the crude product that was used directly in next step without further purification. LCMS calculated for  $\text{C}_{12}\text{H}_{16}\text{BrFNO}_2$  ( $\text{M}+\text{H}$ )<sup>+</sup>  $m/z$ =304.0; found 304.0.

Step 4. 7-Bromo-6-fluoro-8-methylisoquinoline

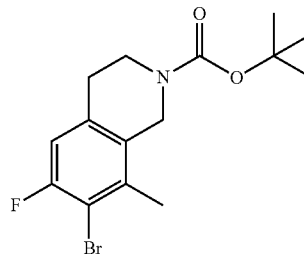
[0833]



[0834] To a solution of 1-(3-bromo-4-fluoro-2-methylphenyl)-N-(2,2-dimethoxyethyl)methanimine (crude in step 3) in THF (100.0 ml) at  $-10^\circ\text{C}$ . was added ethyl chloroformate (3.126 g, 28.8 mmol) dropwise. The mixture was stirred at  $-10^\circ\text{C}$ . for 10 mins, and then allowed to warm to room temperature and stirred for 2 h. Trimethyl phosphite (4.562 g, 36.8 mmol) was added. The mixture was stirred at room temperature for 24 h, and then concentrated. The resulting oil was re-evaporated three times with toluene to remove traces of trimethyl phosphite. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (100.0 ml). A solution of  $\text{TiCl}_4$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ ) (200.0 ml, 200 mmol) was added. The mixture was refluxed under  $\text{N}_2$  for 72 h. After cooling to room temperature, the mixture was poured into ice and treated with ammonium hydroxide (14.8 M in water) until pH reached 10. The mixture was filtered through a pad of Celite. The pad was rinsed with  $\text{CH}_2\text{Cl}_2$ . The organic layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (3.378 g, 50% over 2 steps). LCMS calculated for  $\text{C}_{10}\text{H}_8\text{BrFN}$  ( $\text{M}+\text{H}$ )<sup>+</sup>  $m/z$ =240.0; found 240.0.

Step 5. tert-Butyl 7-bromo-6-fluoro-8-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate

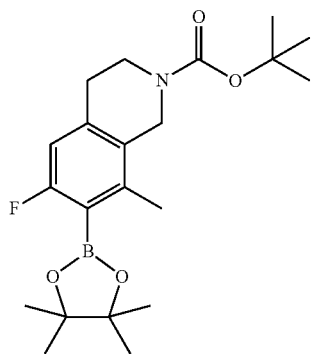
[0835]



[0836] To a solution of 7-bromo-6-fluoro-8-methylisoquinoline (3.378 g, 14.07 mmol) in acetic acid (100.0 ml) at room temperature was added sodium tetrahydroborate (2042.3 mg, 54.0 mmol) portion wise. The mixture was stirred at room temperature for 1 h, and MeOH (100 ml) was added. The mixture was concentrated. The residue was diluted with  $\text{CH}_2\text{Cl}_2$ , and washed with 2 M  $\text{K}_2\text{CO}_3$  (aq). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$ . Boc-anhydride (4.27 g, 19.56 mmol) was added followed by DMAP (534.8 mg, 4.38 mmol). After stirring at room temperature for 40 min, the mixture was treated with MeOH (20 ml) and stirred for 2 h. The mixture was then concentrated. The residue was purified on silica gel (120 g, 0-50% EtOAc in hexanes) to give the desired product as a pale yellow solid (2.13 g, 44%). LCMS calculated for  $\text{C}_{11}\text{H}_{12}\text{BrFNO}_2$  ( $\text{M}+\text{H}-\text{C}_4\text{H}_8$ )<sup>+</sup>  $m/z$ =288.0; found: 288.0.

Step 6. tert-Butyl 6-fluoro-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

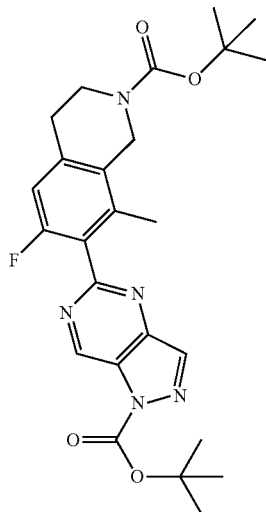
[0837]



[0838] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 7-bromo-6-fluoro-8-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1083.9 mg, 3.15 mmol), 4,4,5,5,4',5',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (1076 mg, 4.24 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (514 mg, 0.630 mmol) and potassium acetate (982.3 mg, 10.01 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (12.0 mL) was added via syringe. The mixture was stirred at 100° C. for 16 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was used directly in the next step.

Step 7. tert-Butyl 7-(1-(tert-butoxycarbonyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6-fluoro-8-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate

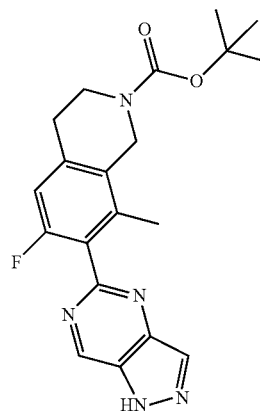
[0839]



[0840] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (882.4 mg, 3.46 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 372.5 mg, 0.473 mmol) and cesium carbonate (3138 mg, 9.63 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 6-fluoro-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (step 6) in 1,4-dioxane (12.0 mL) was added via syringe, followed by water (4.0 mL). The reaction was stirred at 50° C. for 16 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a yellow foamy solid (735.5 mg, 48% over two steps). LCMS calculated for C<sub>25</sub>H<sub>31</sub>FN<sub>5</sub>O<sub>4</sub> (M+H)<sup>+</sup>: m/z=484.2; found: 484.2.

Step 8. tert-Butyl 6-fluoro-8-methyl-7-(1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

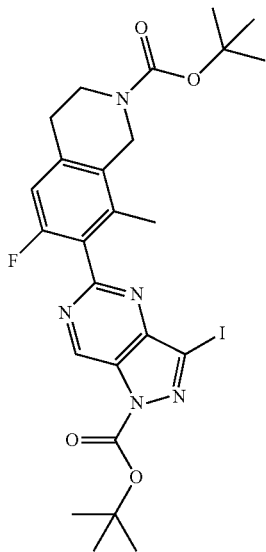
[0841]



[0842] To a solution of tert-butyl 7-(1-(tert-butoxycarbonyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6-fluoro-8-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (735.5 mg, 1.521 mmol) in 1,4-dioxane (8.0 mL) was added potassium carbonate (1552 mg, 11.23 mmol) followed by water (8.0 mL). The mixture was stirred at 80° C. for 10 h. After cooling to room temperature, the mixture was diluted with Et<sub>2</sub>O and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the crude product as a yellow solid that was used directly in the next step without further purification. C<sub>20</sub>H<sub>23</sub>FN<sub>5</sub>O<sub>2</sub> (M+H)<sup>+</sup>: m/z=384.2; found: 384.1.

Step 9. tert-Butyl 7-(1-(tert-butoxycarbonyl)-3-iodo-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6-fluoro-8-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate

[0843]



[0844] To a solution of tert-butyl 6-fluoro-8-methyl-7-(1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (step 8) in DMF (10.0 ml) was added N-iodosuccinimide (412.4 mg, 1.833 mmol). The mixture was stirred at 60° C. for 90 mins, and cooled to room temperature. Boc-anhydride (494.2 mg, 2.264 mmol) was added followed by DMAP (77.8 mg, 0.637 mmol). The reaction was stirred at room temperature for 30 mins. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with sat. NaHCO<sub>3</sub>(aq). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product (198.1 mg, 21% over 2 steps). LCMS calculated for C<sub>25</sub>H<sub>30</sub>FIN<sub>5</sub>O<sub>4</sub> (M+H)<sup>+</sup>: m/z=610.1; found: 610.1.

Step 10. 6-Fluoro-8-methyl-7-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

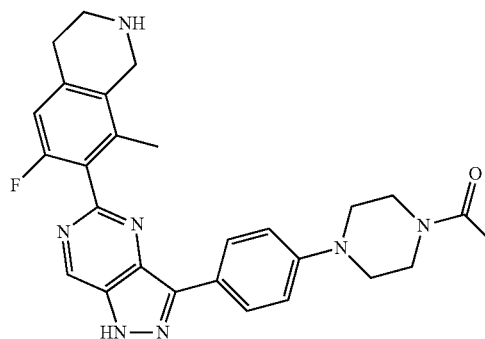
[0845] To a screw-cap vial equipped with a magnetic stir bar was added 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (18.0 mg, 0.059 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 5.0 mg, 6.35 μmol) and cesium carbonate (50.1 mg, 0.154 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 7-(1-(tert-butoxycarbonyl)-3-iodo-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6-fluoro-8-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (25.0 mg, 0.041 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0 μl). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred

at room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>25</sub>H<sub>28</sub>FN<sub>8</sub> (M+H)<sup>+</sup>: m/z=459.2; found: 459.2.

#### Example 108

1-(4-(4-(5-(6-Fluoro-8-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperazin-1-yl)ethanone

[0846]

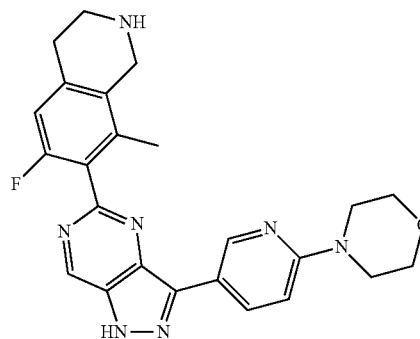


[0847] This compound was prepared according to the procedure described in Example 107 (step 10), using 1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-1-yl)ethanone instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for C<sub>27</sub>H<sub>29</sub>FN<sub>7</sub>O (M+H)<sup>+</sup>: m/z=486.2; found: 486.3.

#### Example 109

4-(5-(5-(6-Fluoro-8-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)morpholine

[0848]



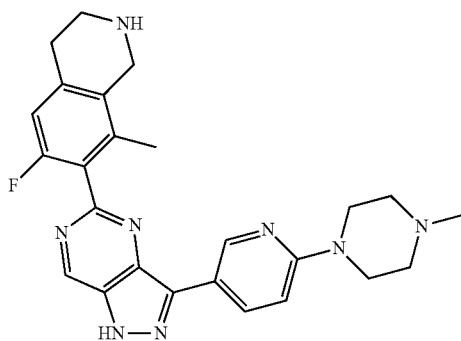
[0849] This compound was prepared according to the procedure described in Example 107 (step 10), using 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the

starting material. LCMS calculated for  $C_{24}H_{25}FN_7O$  ( $M+H$ )<sup>+</sup>:  $m/z=446.2$ ; found: 446.3.

### Example 110

6-Fluoro-8-methyl-7-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0850]

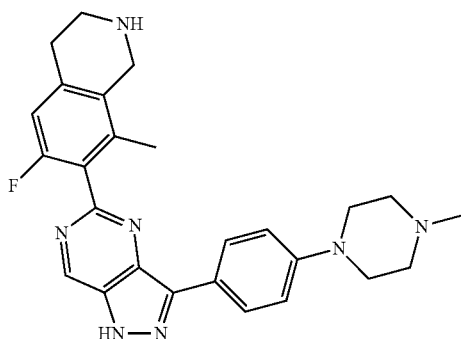


[0851] This compound was prepared according to the procedure described in Example 107 (step 10), using 1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{25}H_{28}FN_8$  ( $M+H$ )<sup>+</sup>:  $m/z=459.2$ ; found: 459.2.

### Example 111

6-Fluoro-8-methyl-7-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0852]



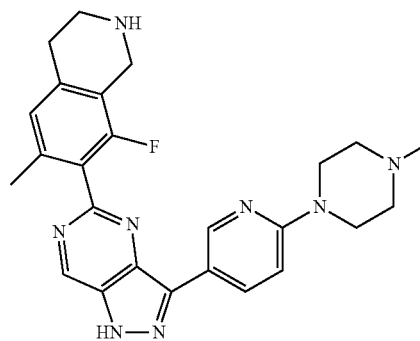
[0853] This compound was prepared according to the procedure described in Example 107 (step 10), using 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine as the starting material. LCMS calculated for  $C_{26}H_{29}FN_7$  ( $M+H$ )<sup>+</sup>:  $m/z=458.2$ ; found: 458.3. <sup>1</sup>H NMR (TFA salt, 500 MHz, DMSO)  $\delta$  10.14 (br, 1H), 9.46 (s, 1H), 9.36 (br, 2H), 8.29 (d,  $J=8.9$  Hz, 2H), 7.14 (m, 3H), 4.25 (s, 2H), 3.93 (m,

2H), 3.52 (m, 2H), 3.40 (m, 2H), 3.16 (m, 2H), 3.09 (t,  $J=6.1$  Hz, 2H), 3.03 (m, 2H), 2.86 (s, 3H), 1.98 (s, 3H).

### Example 112

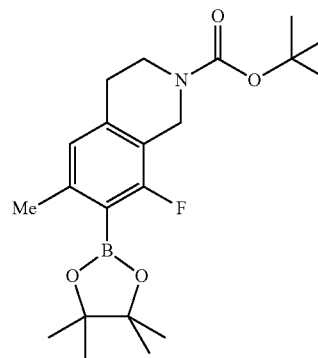
8-Fluoro-6-methyl-7-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

[0854]



Step 1. tert-Butyl 8-fluoro-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[0855]



[0856] This compound was prepared according to the procedures described in Example 107 (step 3 to step 6), using 3-bromo-2-fluoro-4-methylbenzaldehyde (AstaTech) instead of 3-bromo-4-fluoro-2-methylbenzaldehyde (step 2 in Example 107) as the starting material. LCMS calculated for  $C_{21}H_{31}BFNNaO_4$  ( $M+Na$ )<sup>+</sup>:  $m/z=414.2$ ; found: 414.2.

Step 2. 8-Fluoro-6-methyl-7-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline

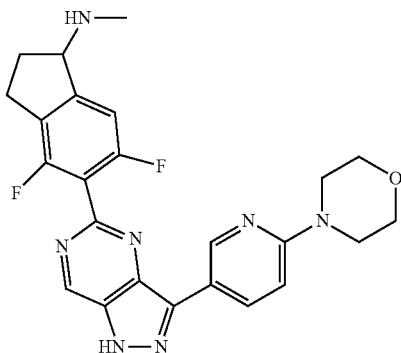
[0857] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (42.8 mg, 0.100 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 9.0 mg, 0.011

mmol) and cesium carbonate (84.3 mg, 0.259 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl 8-fluoro-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (31.7 mg, 0.081 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added  $\text{CH}_2\text{Cl}_2$  (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for  $\text{C}_{25}\text{H}_{28}\text{FN}_8$  ( $\text{M}+\text{H}^+$ ):  $m/z=459.2$ ; found: 459.2.  $^1\text{H}$  NMR (TFA salt, 600 MHz, DMSO)  $\delta$  10.09 (br, 1H), 9.49 (s, 1H), 9.29 (br, 2H), 9.20-9.18 (m, 1H), 8.48 (dd,  $J=8.8, 2.3$  Hz, 1H), 7.13 (d,  $J=8.8$  Hz, 1H), 7.11 (s, 1H), 4.48 (m, 2H), 4.31 (s, 2H), 3.52 (m, 2H), 3.46-3.36 (m, 2H), 3.20 (m, 2H), 3.06 (m, 4H), 2.84 (s, 3H), 2.17 (s, 3H).

#### Example 113

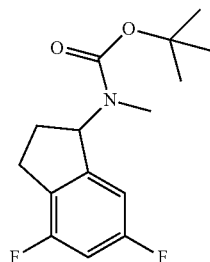
4,6-Difluoro-N-methyl-5-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

[0858]



Step 1. tert-Butyl 4,6-difluoro-2,3-dihydro-1H-inden-1-yl(methyl)carbamate

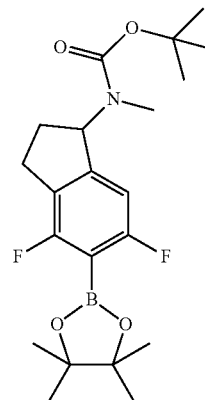
[0859]



[0860] To a solution of 4,6-difluoro-2,3-dihydro-1H-inden-1-one (Ark Pharm, 4.015 g, 23.88 mmol) in 2-propanol (90.0 ml) was added methylamine (2.0 M in methanol) (60.0 ml, 120 mmol) followed by titanium(IV) isopropoxide (15.31 ml, 51.7 mmol). The mixture was stirred at 35° C. for 16 h before it was cooled to room temperature. Sodium borohydride (1.312 g, 34.7 mmol) was added. The reaction was stirred at room temperature for 1 h, and was quenched with HCl (6.0 N in water) (60.0 ml, 360 mmol). The mixture was stirred at room temperature for 2 h, and was treated with NaOH (4.0 N in water) until pH reached 10. The mixture was extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL), and treated with boc-anhydride (5.21 g, 23.88 mmol). After stirring at room temperature for 30 min, the reaction was concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as an oil (5.27 g, 78%). LCMS calculated for  $\text{C}_{11}\text{H}_{12}\text{F}_2\text{NO}_2$  ( $\text{M}+\text{H}-\text{C}_4\text{H}_8$ ) $^+$ :  $m/z=228.1$ ; found: 228.1.

Step 2. tert-Butyl 4,6-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yl(methyl)carbamate

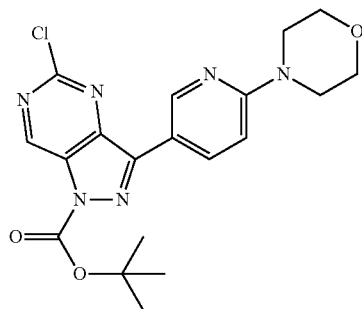
[0861]



[0862] To a solution of tert-butyl (4,6-difluoro-2,3-dihydro-1H-inden-1-yl)(methyl)carbamate (5.27 g, 18.60 mmol) in THF (100.0 ml) at -78° C. under  $\text{N}_2$  was added a solution of n-BuLi (2.5 M in hexanes) (15.00 ml, 37.5 mmol) slowly over a period of 20 min. The reaction was allowed to warm to -60° C. and stirred for 90 min. The reaction was then cooled back to -78° C. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.79 g, 58.0 mmol) was added slowly over a period of 20 min. After stirring at -78° C. for another 10 min, the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with sat.  $\text{NaHCO}_3$ , and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as an oil (1.74 g, 23%). LCMS calculated for  $\text{C}_{17}\text{H}_{23}\text{BF}_2\text{NO}_4$  ( $\text{M}+\text{H}-\text{C}_4\text{H}_8$ ) $^+$ :  $m/z=354.2$ ; found: 354.1.

Step 3. tert-Butyl 5-chloro-3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

[0863]



[0864] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (463.9 mg, 1.219 mmol), 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (468.2 mg, 1.614 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complexed with dichloromethane (1:1) (149.2 mg, 0.183 mmol) and cesium carbonate (1.2 g, 3.69 mmol). The vial was sealed with a Teflon-lined septum, evacuated and back-filled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (10.0 ml) was added, followed by water (3.0 ml). The reaction was stirred at 50° C. for 4 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a yellow solid (395.2 mg, 78%). LCMS calculated for C<sub>19</sub>H<sub>22</sub>ClN<sub>6</sub>O<sub>3</sub> (M+H)<sup>+</sup> m/z=417.1; found 417.1.

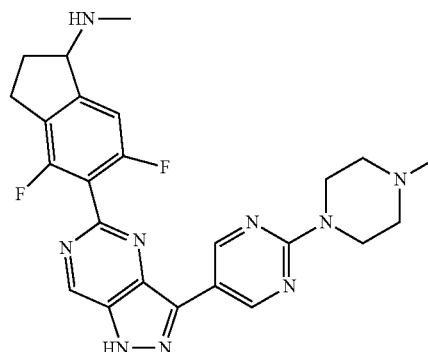
Step 4. 4,6-Difluoro-N-methyl-5-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

[0865] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (24.8 mg, 0.059 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 5.6 mg, 7.12 μmol) and cesium carbonate (58.6 mg, 0.180 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (4,6-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yl)(methyl)carbamate (24.8 mg, 0.061 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0 μl). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>24</sub>H<sub>24</sub>F<sub>2</sub>N<sub>7</sub>O (M+H)<sup>+</sup> m/z=464.2; found: 464.2.

Example 114

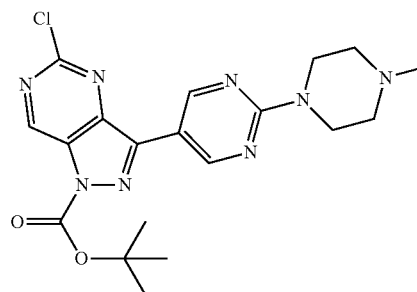
4,6-Difluoro-N-methyl-5-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

[0866]



Step 1. tert-Butyl 5-chloro-3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate

[0867]



[0868] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-iodo-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (1026.0 mg, 2.70 mmol), 2-(4-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (816.5 mg, 2.68 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (330.2 mg, 0.404 mmol) and cesium carbonate (2.693 g, 8.27 mmol). The vial was sealed with a Teflon-lined septum, evacuated and back-filled with nitrogen (this process was repeated a total of three times). 1,4-Dioxane (12.0 ml) was added, followed by water (4.0 ml). The reaction was stirred at 50° C. for 16 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes, then 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give the desired product as a yellow foamy solid (877.3 mg, 76%). LCMS calculated for C<sub>19</sub>H<sub>24</sub>ClN<sub>8</sub>O<sub>2</sub> (M+H)<sup>+</sup> m/z=431.2; found 431.1.

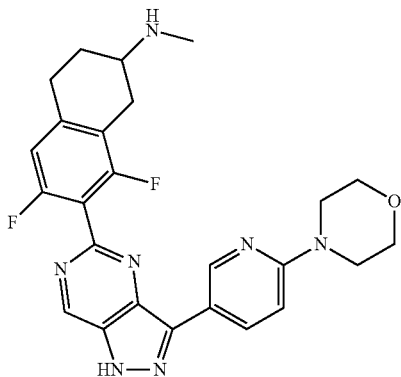
Step 2. 4,6-Difluoro-N-methyl-5-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

**[0869]** To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (81.4 mg, 0.189 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 28.4 mg, 0.036 mmol) and cesium carbonate (110.9 mg, 0.340 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (4,6-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yl)(methyl)carbamate (64.0 mg, 0.156 mmol) in 1,4-dioxane (3.00 ml) was added via syringe, followed by water (300.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>24</sub>H<sub>26</sub>F<sub>2</sub>N<sub>9</sub> (M+H)<sup>+</sup>: m/z=478.2; found: 478.2.

#### Example 115

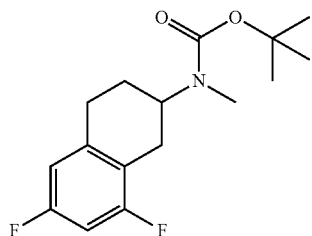
6,8-Difluoro-N-methyl-7-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-2-amine

**[0870]**



Step 1. tert-Butyl 6,8-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl(methyl)carbamate

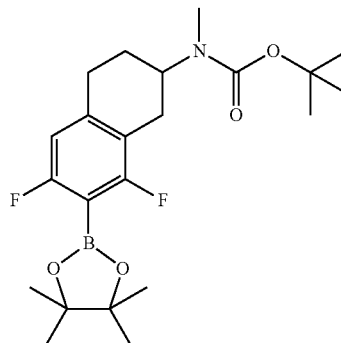
**[0871]**



**[0872]** To a solution of 6,8-difluoro-3,4-dihydronaphthalen-2(1H)-one (Ark Pharm, 1.316 g, 7.22 mmol) in MeOH (30.0 ml) was added methylamine hydrochloride (5.38 g, 80 mmol), sodium cyanoborohydride (2.398 g, 38.2 mmol) and THF (30.0 ml). The mixture was heated to 50° C. for 16 h. After cooling to room temperature, the mixture was quenched with HCl (6.0 N in water) (30.0 ml, 180 mmol). The mixture was stirred at room temperature for 2 h, and was treated with NaOH (4.0 N in water) until pH reached 10. The mixture was extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and treated with Boc-anhydride (1.548 g, 7.09 mmol). After stirring at room temperature for 30 min, the reaction was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (1.177 g, 55%). LCMS calculated for C<sub>12</sub>H<sub>14</sub>F<sub>2</sub>NO<sub>2</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup>: m/z=242.1; found: 242.1.

Step 2. tert-Butyl 6,8-difluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl(methyl)carbamate

**[0873]**



**[0874]** To a solution of tert-butyl (6,8-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl)(methyl)carbamate (1.177 g, 3.96 mmol) in THF (30.0 ml) at -78° C. under N<sub>2</sub> was added a solution of n-BuLi (2.5 M in hexanes) (3.20 ml, 8.00 mmol) slowly over a period of 20 mins. The reaction was allowed to warm to -60° C. and stirred for 60 mins. The reaction was then cooled back to -78° C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.425 ml, 11.89 mmol) in THF (10.0 mL) was added slowly over a period of 20 mins. After stirring at -78° C. for 20 mins, the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with sat. NaHCO<sub>3</sub>, and extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (922.0 mg, 55%). LCMS calculated for C<sub>22</sub>H<sub>32</sub>BF<sub>2</sub>NNaO<sub>4</sub> (M+Na)<sup>+</sup>: m/z=446.2; found: 446.2.

Step 3. 6,8-Difluoro-N-methyl-7-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-2-amine

**[0875]** To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-morpholinopyridin-

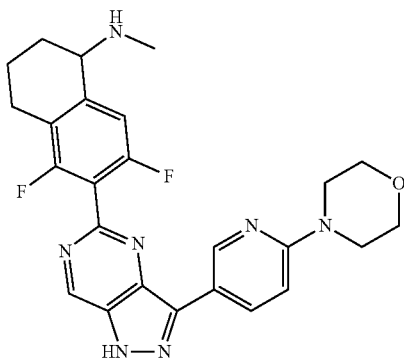


3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (24.8 mg, 0.059 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 7.0 mg, 8.90  $\mu$ mol) and cesium carbonate (58.5 mg, 0.180 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (6,8-difluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl) (methyl)carbamate (22.3 mg, 0.053 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>25</sub>H<sub>26</sub>F<sub>2</sub>N<sub>7</sub>O (M+H)<sup>+</sup>: m/z=478.2; found: 478.3.

#### Example 116

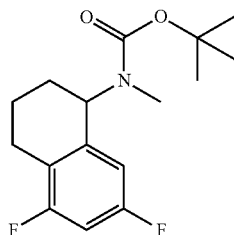
5,7-Difluoro-N-methyl-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

[0876]



Step 1. tert-Butyl 5,7-difluoro-1,2,3,4-tetrahydronaphthalen-1-yl(methyl)carbamate

[0877]

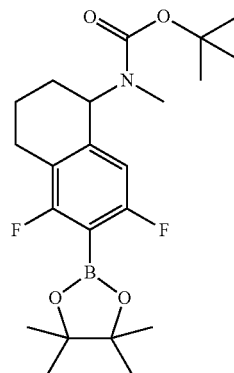


[0878] To a solution of 5,7-difluoro-3,4-dihydronaphthalen-1(2H)-one (Ark Pharm, 1.325 g, 7.27 mmol) in 2-propanol (30.0 ml) was added methylamine (2.0 M in methanol) (15.00 ml, 30.0 mmol) followed by titanium(IV) isopropox-

ide (4.06 ml, 13.73 mmol) and THF (15.0 ml). The mixture was stirred at 35° C. for 16 h before it was cooled to room temperature. Sodium borohydride (418.4 mg, 11.06 mmol) was added. The reaction was stirred at room temperature for 1 h, and was quenched with HCl (6.0 N in water) (40.0 ml, 240 mmol). The mixture was stirred at room temperature for 2 h, and was treated with NaOH (4.0 N in water) until pH reached 10. The mixture was extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL), and treated with Boc-anhydride (1.709 g, 7.83 mmol). After stirring at room temperature for 30 mins, the reaction was concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product (1.873 g, 87%). LCMS calculated for C<sub>12</sub>H<sub>14</sub>F<sub>2</sub>NO<sub>2</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup>: m/z=242.1; found: 242.1.

Step 2. tert-Butyl 5,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl(methyl)carbamate

[0879]



[0880] To a solution of tert-butyl (5,7-difluoro-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (1.872 g, 6.30 mmol) in THF (40.0 ml) at -78° C. under N<sub>2</sub> was added a solution of n-BuLi (2.5 M in hexanes) (5.00 ml, 12.50 mmol) slowly over a period of 20 mins. The reaction was allowed to warm to -60° C. and stirred for 60 mins. The reaction was then cooled back to -78° C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.85 ml, 18.89 mmol) in THF (10.0 mL) was added slowly over a period of 20 mins. After stirring at -78° C. for 20 mins, the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with sat. NaHCO<sub>3</sub>, and extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a yellow foamy solid (989.9 mg, 37%). LCMS calculated for C<sub>22</sub>H<sub>32</sub>BF<sub>2</sub>NNaO<sub>4</sub> (M+Na)<sup>+</sup>: m/z=446.2; found: 446.2.

Step 3. 5,7-Difluoro-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

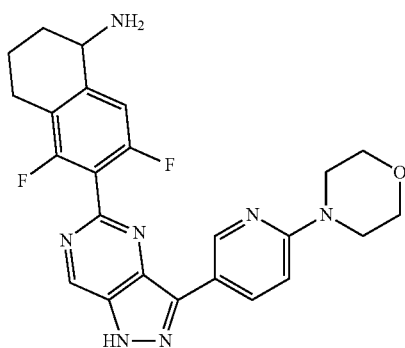
[0881] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (24.8

mg, 0.059 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 7.0 mg, 8.90  $\mu$ mol) and cesium carbonate (59.7 mg, 0.183 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (5,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl) (methyl)carbamate (23.3 mg, 0.055 mmol) in 1,4-dioxane (2.00 ml) was added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated C<sub>25</sub>H<sub>26</sub>F<sub>2</sub>N<sub>7</sub>O (M+H)<sup>+</sup>: m/z=478.2; found: 478.2

## Example 117

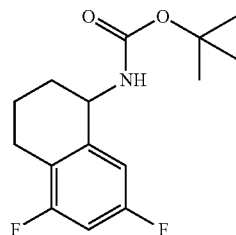
5,7-Difluoro-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

[0882]



Step 1. tert-Butyl 5,7-difluoro-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

[0883]

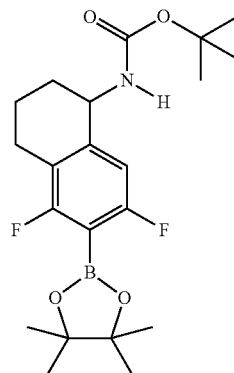


[0884] To a mixture of 5,7-difluoro-3,4-dihydronaphthalen-1(2H)-one (Ark Pharm, 1636.4 mg, 8.98 mmol), sodium cyanoborohydride (6.064 g, 96 mmol) and ammonium acetate (16.51 g, 214 mmol) was added 2-propanol (50.0 ml). The reaction was stirred at 70° C. for 16 h. After cooling

to room temperature, the mixture was diluted with water and extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was dissolved in THF (100 ml), and HCl (6.0 N in water) (50.0 ml, 300 mmol) was added. The mixture was stirred at room temperature for 16 h, and was treated with NaOH (4.0 N in water) until pH reached 10. The mixture was extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 ml), and was treated with boc-anhydride (1.982 g, 9.08 mmol). After stirring at room temperature for 30 mins, the reaction was concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (1.836 g, 72%). LCMS calculated for C<sub>11</sub>H<sub>12</sub>F<sub>2</sub>NO<sub>2</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup>: m/z=228.1; found: 228.1.

Step 2. tert-Butyl 5,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

[0885]



[0886] To a solution of tert-butyl (5,7-difluoro-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (1.836 g, 6.48 mmol) in THF (40.0 ml) at -78° C. under N<sub>2</sub> was added a solution of n-BuLi (2.5 M in hexanes) (7.00 ml, 17.50 mmol) slowly via syringe over a period of 20 mins. The reaction was allowed to warm to -60° C. and stirred for 60 mins. The reaction was then cooled back to -78° C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.04 ml, 24.72 mmol) in THF (10.0 ml) was added via syringe slowly over a period of 20 mins. After stirring at -78° C. for 20 mins, the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with sat. NaHCO<sub>3</sub>, and extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a white foamy solid (1.632 g, 62%). LCMS calculated for C<sub>21</sub>H<sub>30</sub>BF<sub>2</sub>NNaO<sub>4</sub> (M+Na)<sup>+</sup>: m/z=432.2; found: 432.2.

Step 3. 5,7-Difluoro-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

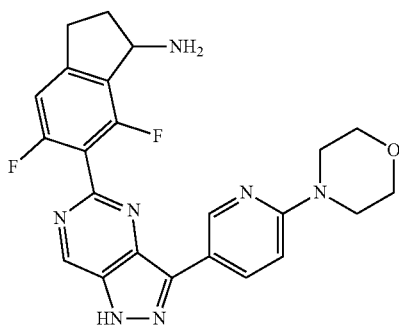
[0887] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (28.5

mg, 0.068 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 8.0 mg, 10.17  $\mu$ mol) and cesium carbonate (66.8 mg, 0.205 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (5,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl) carbamate (24.7 mg, 0.060 mmol) in 1,4-Dioxane (2.00 ml) was added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for C<sub>24</sub>H<sub>24</sub>F<sub>2</sub>N<sub>7</sub>O (M+H)<sup>+</sup>: m/z=464.2; found: 464.2.

### Example 118

5,7-Difluoro-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

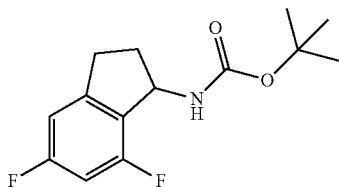
[0888]



### Step 1. tert-Butyl

5,7-dilltioro-2,3-dihydro-1H-inden-1-ylcarbamate

[0889]

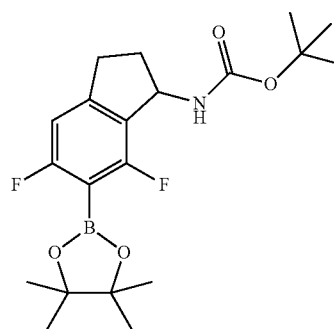


[0890] To a solution of boc-anhydride (1.398 g, 6.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15.0 ml) was added 5,7-difluoro-2,3-dihydro-1H-inden-1-amine, HCl salt (AstaTech, 1.002 g,

4.87 mmol) followed by N,N-diisopropylethylamine (2.93 ml, 16.78 mmol). The mixture was stirred at room temperature for 30 min, and then concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (1.178 g, 90%).

Step 2. tert-Butyl 5,7-dilltioro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-ylcarbamate

[0891]



[0892] To a solution of tert-butyl (5,7-difluoro-2,3-dihydro-1H-inden-1-yl)carbamate (1.168 g, 4.34 mmol) in THF (40.0 ml) at -78° C. under N<sub>2</sub> was added a solution of n-BuLi (2.5 M in hexanes) (4.60 ml, 11.50 mmol) slowly via syringe over a period of 20 mins. The reaction was allowed to warm to -60° C. and stirred for 60 mins. The reaction was then cooled back to -78° C. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.01 ml, 14.77 mmol) was added slowly via syringe over a period of 20 mins. After stirring at -78° C. for 20 min, the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with sat. NaHCO<sub>3</sub>, and extracted with Et<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a white foamy solid (893.5 mg, 52%). LCMS calculated for C<sub>20</sub>H<sub>28</sub>BF<sub>2</sub>NNaO<sub>4</sub> (M+Na)<sup>+</sup>: m/z=418.2; found: 418.2.

Step 3. 5,7-Dilltioro-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

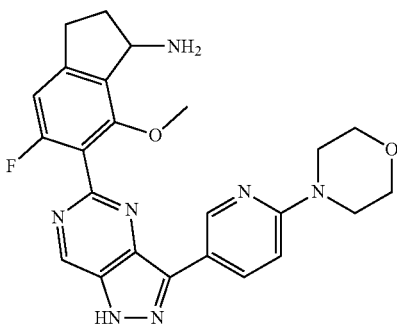
[0893] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (28.5 mg, 0.068 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 8.0 mg, 10.17  $\mu$ mol) and cesium carbonate (70.0 mg, 0.215 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (5,7-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yl)carbamate (24.9 mg, 0.063 mmol) in 1,4-dioxane (2.00 ml) was

added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added  $\text{CH}_2\text{Cl}_2$  (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for  $\text{C}_{23}\text{H}_{22}\text{F}_2\text{N}_7\text{O}$  ( $\text{M}+\text{H}$ )<sup>+</sup>:  $m/z=450.2$ ; found: 450.3.

#### Example 119

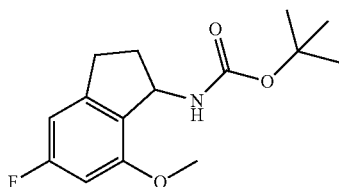
5-Fluoro-7-methoxy-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

[0894]



Step 1. tert-Butyl 5-fluoro-7-methoxy-2,3-dihydro-1H-inden-1-ylcarbamate

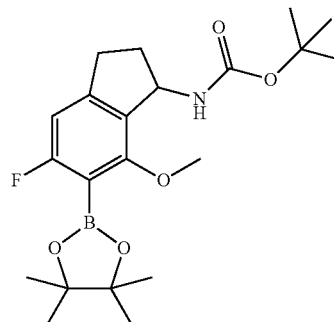
[0895]



[0896] To a mixture of 5-fluoro-7-methoxy-2,3-dihydro-1H-inden-1-one (NetChem, 1742.0 mg, 9.67 mmol), sodium cyanotrihydroborate (6212.9 mg, 99 mmol) and ammonium acetate (18.12 g, 235 mmol) was added 2-propanol (60.0 mL). The reaction was stirred at 70° C. for 16 h. After cooling to room temperature, the mixture was diluted with 2 N NaOH(aq) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $\times 10$ ). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (40 mL), and was treated with boc-anhydride (2.156 g, 9.88 mmol). After stirring at room temperature for 30 mins, the reaction was concentrated. The residue was purified on silica gel (120 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (1.886 g, 69%). LCMS calculated for  $\text{C}_{11}\text{H}_{13}\text{FNO}_3$  ( $\text{M}+\text{H}-\text{C}_4\text{H}_8$ )<sup>+</sup>:  $m/z=226.1$ ; found: 226.1.

Step 2. tert-Butyl 5-fluoro-7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-ylcarbamate

[0897]



[0898] To a solution of tert-butyl (5-fluoro-7-methoxy-2,3-dihydro-1H-inden-1-yl)carbamate (1.886 g, 6.70 mmol) in THF (40.0 mL) at -78° C. under  $\text{N}_2$  was added a solution of n-BuLi (2.5 M in hexanes) (7.50 mL, 18.75 mmol) slowly via syringe over a period of 20 mins. The reaction was allowed to warm to -60° C. and stirred for 60 mins. The reaction was then cooled back to -78° C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.00 mL, 24.51 mmol) was added slowly via syringe over a period of 20 mins. After stirring at -78° C. for 20 mins, the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with sat.  $\text{NaHCO}_3$ , and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified on silica gel (40 g, 0-50% EtOAc in hexanes) to give the desired product as a white foamy solid (1.063 g, 39%). LCMS calculated for  $\text{C}_{21}\text{H}_{31}\text{BFNNaO}_5$  ( $\text{M}+\text{Na}$ )<sup>+</sup>:  $m/z=430.2$ ; found: 430.2.

Step 3. 5-Fluoro-7-methoxy-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine

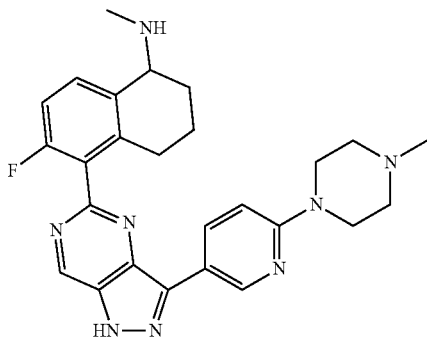
[0899] To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 5-chloro-3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (28.5 mg, 0.068 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 8.0 mg, 10.17  $\mu$ mol) and cesium carbonate (69.8 mg, 0.214 mmol). The vial was sealed with a Teflon-lined septum, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (5-fluoro-7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yl)carbamate (25.8 mg, 0.063 mmol) in 1,4-dioxane (2.00 mL) was added via syringe, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was concentrated. To the residue was added  $\text{CH}_2\text{Cl}_2$  (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for  $\text{C}_{24}\text{H}_{25}\text{FN}_7\text{O}_2$  ( $\text{M}+\text{H}$ )<sup>+</sup>:  $m/z=462.2$ ; found: 462.1.  $^1\text{H}$  NMR (TFA salt, 600 MHz, DMSO)  $\delta$  9.49 (s, 1H), 9.17-9.14 (m, 1H), 8.44 (dd, J=9.0,

2.4 Hz, 1H), 8.15 (br, 3H), 7.10 (d, J=8.9 Hz, 1H), 7.04 (d, J=9.0 Hz, 1H), 4.91 (m, 1H), 3.72-3.69 (m, 4H), 3.55-3.51 (m, 4H), 3.46 (s, 3H), 3.17 (m, 1H), 3.01-2.89 (m, 1H), 2.59-2.52 (m, 1H), 2.08 (m, 1H).

### Example 120

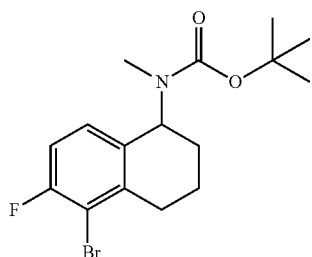
6-Fluoro-N-methyl-5-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

[0900]



Step 1. tert-Butyl 5-bromo-6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl(methyl)carbamate

[0901]

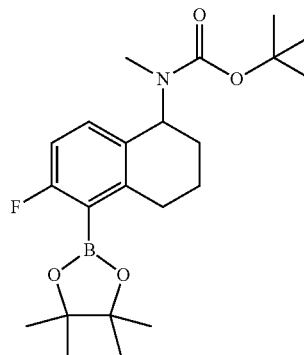


[0902] To a solution of 5-bromo-6-fluoro-3,4-dihydronaphthalen-1(2H)-one (Ark Pharm, 312.6 mg, 1.286 mmol) in 2-propanol (10.0 ml) was added methylamine (2.0 M in methanol) (2.50 ml, 5.00 mmol) followed by titanium (IV) isopropoxide (596.0 mg, 2.097 mmol). The mixture was stirred at 35° C. for 16 h before it was cooled to room temperature. Sodium borohydride (53.4 mg, 1.412 mmol) was added. The reaction was stirred at room temperature for 1 h, and was treated with HCl (1.0 N in water) (30.0 ml, 30 mmol). The mixture was stirred at room temperature for 2 h, and was treated with NaOH (4.0 N in water) until the pH reached 10. The mixture was extracted with Et<sub>2</sub>O. The organic phase was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml), and treated with boc-anhydride (426.4 mg, 1.954 mmol). After stirring at room temperature for 30 min, the reaction was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the

desired product (461.0 mg, 89%). LCMS calculated for C<sub>12</sub>H<sub>14</sub>BrFNO<sub>2</sub> (M+H—C<sub>4</sub>H<sub>8</sub>)<sup>+</sup>: m/z=302.0; found: 302.1.

Step 2. tert-Butyl 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl(methyl)carbamate

[0903]



[0904] A vial was charged with 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (517.4 mg, 2.037 mmol), potassium acetate (416.8 mg, 4.25 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complexed with dichloromethane (1:1) (210.2 mg, 0.257 mmol). The vial was sealed, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (5-bromo-6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (461.0 mg, 1.287 mmol) in 1,4-dioxane (6.0 ml) was added, and the mixture was heated at 100° C. for 16 h. After cooling to room temperature, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and filtered. The filtrate was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product (337.4 mg, 65%). LCMS calculated for C<sub>22</sub>H<sub>33</sub>BFNNaO<sub>4</sub> (M+Na)<sup>+</sup> m/z=428.2; found 428.2.

Step 3. 6-Fluoro-N-methyl-5-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

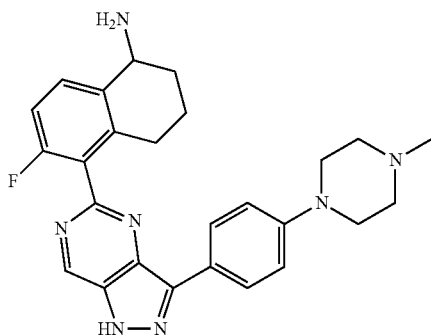
[0905] A vial was charged with tert-butyl 5-chloro-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (34.0 mg, 0.079 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 8.0 mg, 10.17 μmol) and cesium carbonate (81.4 mg, 0.250 mmol). The vial was sealed, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (28.1 mg, 0.069 mmol) in 1,4-dioxane (2.0 ml) was added, followed by water (200.0 μl). The reaction mixture was heated to 50° C. for 16 h., cooled and concentrated. To the residue was added CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 mins, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1%

TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated  $C_{26}H_{30}FN_8$  (M+H)<sup>+</sup>: m/z=473.3; found: 473.3.

### Example 121

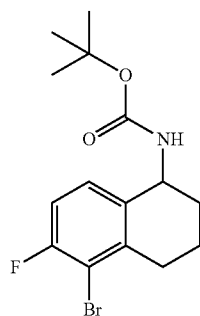
6-Fluoro-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

[0906]



Step 1. tert-Butyl 5-bromo-6-fluoro-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

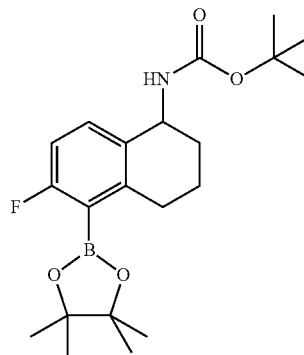
[0907]



[0908] To a mixture of 5-bromo-6-fluoro-3,4-dihydronaphthalen-1(2H)-one (Ark Pharm, 309.5 mg, 1.273 mmol), sodium cyanoborohydride (824.0 mg, 13.11 mmol) and ammonium acetate (2.184 g, 28.3 mmol) was added 2-propanol (10.0 ml). The reaction was stirred at 70° C. for 16 h. After cooling to room temperature, the mixture was diluted with 2 M  $K_2CO_3$  (aq) and extracted with  $Et_2O$ . The organic phase was separated, was dried over anhydrous  $Na_2SO_4$ , filtered and concentrated. The residue was dissolved in  $CH_2Cl_2$  (20 ml), and was treated with Boc-anhydride (425.9 mg, 1.951 mmol). After stirring at room temperature for 30 min, the reaction mixture was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product as a white solid (316.3 mg, 72%). LCMS calculated for  $C_{11}H_{12}BrFNO_2$  (M+H— $C_4H_8$ )<sup>+</sup>: m/z=288.0; found: 288.0.

Step 2. tert-Butyl 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate

[0909]



[0910] A vial was charged with 4,4,5,5,4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (319.0 mg, 1.256 mmol), potassium acetate (272.1 mg, 2.77 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (150.1 mg, 0.184 mmol). The vial was sealed, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (5-bromo-6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (316.3 mg, 0.919 mmol) in 1,4-dioxane (6.0 ml) was added. The mixture was heated at 100° C. for 16 h. After cooling to room temperature, the reaction mixture was diluted with  $CH_2Cl_2$  and filtered. The filtrate was concentrated. The residue was purified on silica gel (40 g, 0-100% EtOAc in hexanes) to give the desired product (200.0 mg, 56%). LCMS calculated for  $C_{17}H_{24}BFNO_4$  (M+H— $C_4H_8$ )<sup>+</sup>: m/z=336.2; found: 336.3.

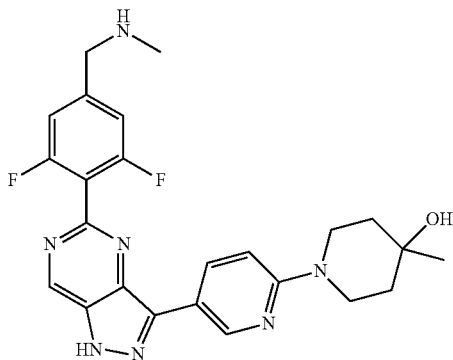
Step 3. 6-Fluoro-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine

[0911] A vial was charged with tert-butyl 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine-1-carboxylate (30.0 mg, 0.070 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2, 8.0 mg, 10.17  $\mu$ mol) and cesium carbonate (72.8 mg, 0.223 mmol). The vial was sealed, evacuated and backfilled with nitrogen (this process was repeated a total of three times). A solution of tert-butyl (6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (25.0 mg, 0.064 mmol) in 1,4-dioxane (2.00 ml) was added, followed by water (200.0  $\mu$ l). The reaction was heated to 50° C. for 16 h. The reaction was cooled and concentrated. To the residue was added  $CH_2Cl_2$  (2.0 mL) followed by TFA (2.0 mL). The mixture was stirred at room temperature for 15 min, and then concentrated. The residue was purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LCMS calculated for  $C_{26}H_{29}FN_7$  (M+H)<sup>+</sup>: m/z=458.3; found: 458.3.

## Example 122

1-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-4-methylpiperidin-4-ol

[0912]

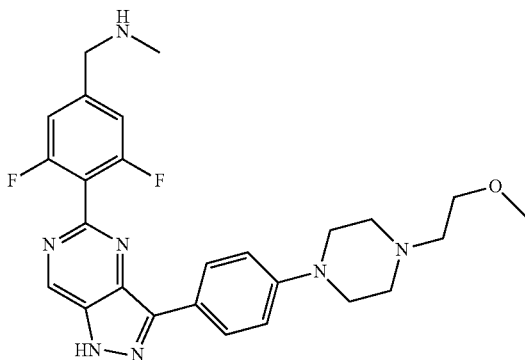


[0913] This compound was prepared according to the procedure described in Example 70, using 4-methylpiperidin-4-ol instead of 2-methyl-1-(piperazin-1-yl)propan-2-ol as starting material. LC-MS calculated for  $C_{24}H_{26}F_2N_7O$  (M+H)<sup>+</sup>: m/z=466.2; Found 466.2.

## Example 123

1-(3,5-Difluoro-4-(3-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine

[0914]

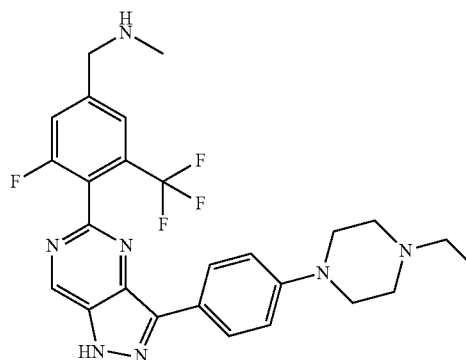


[0915] This compound was prepared according to the procedure described in Example 72, using 1-(2-methoxyethyl)piperazine instead of 1-(methylsulfonyl)piperidin-4-amine as starting material. LC-MS calculated for  $C_{26}H_{30}F_2N_7O$  (M+H)<sup>+</sup>: m/z=494.2; Found 494.2.

## Example 124

1-(4-(3-(4-(4-Ethylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-fluoro-5-(trifluoromethyl)phenyl)-N-methylmethanamine

[0916]

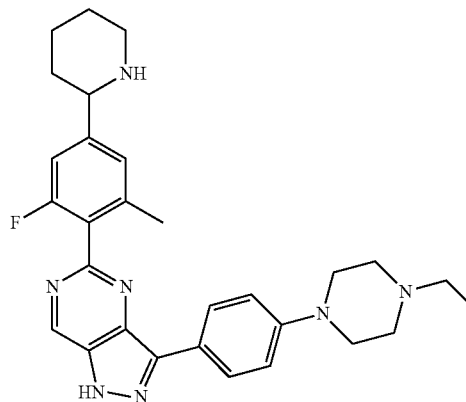


[0917] This compound was prepared according to the procedure described in Example 76, using 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine instead of (6-(piperidin-1-yl)pyridin-3-yl)boronic acid as starting material. LC-MS calculated for  $C_{26}H_{28}F_4N_7$  (M+H)<sup>+</sup>: m/z=514.2; Found 514.2. <sup>1</sup>H NMR (500 MHz, DMSO) δ 9.50 (s, 1H), 9.27 (bs, 1H), 8.30 (d, J=8.9 Hz, 2H), 7.97 (s, 1H), 7.90 (dd, J=9.7, 1.6 Hz, 1H), 7.19-7.14 (m, 2H), 4.38 (s, 2H), 4.02-3.90 (m, 2H), 3.59 (d, J=10.3 Hz, 2H), 3.26-3.17 (q, J=7.3 Hz, 2H), 3.17-3.10 (d, J=20.8 Hz, 2H), 3.08 (s, 2H), 2.69 (s, 3H), 1.27 (t, J=7.2 Hz, 3H).

## Example 125

3-(4-(4-Ethylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methyl-4-(piperidin-2-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

[0918]



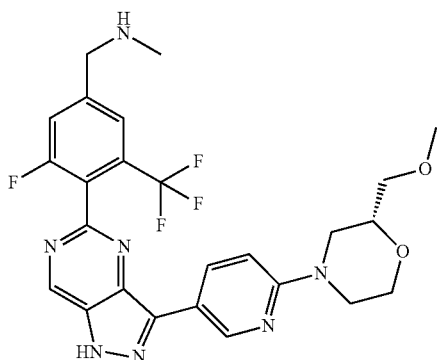
[0919] This compound was prepared according to the procedures described in Example 81, using 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine, instead of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-di-

oxaborolan-2-yl)phenyl)piperazine as starting material. LCMS calculated for  $C_{29}H_{35}FN_7$  (M+H)<sup>+</sup>: m/z=500.3; Found: 500.3.

## Example 126

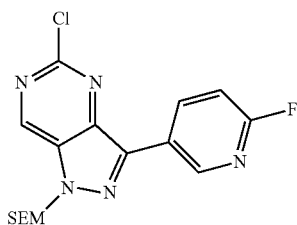
(R)-1-(3-Fluoro-4-(3-(6-(2-(methoxymethyl)morpholino)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)phenyl)-N-methylmethanamine

[0920]



Step 1. 5-Chloro-3-(6-fluoropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine

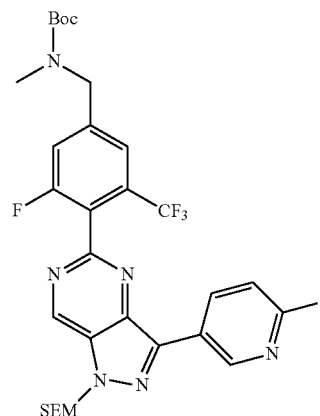
[0921]



[0922] To a solution of 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (Example 1, step 2. 2.60 g, 6.33 mmol) in dioxane (24 ml) and water (6 ml) were added potassium phosphate, tribasic (2.60 g, 12.7 mmol) and (6-fluoropyridin-3-yl)boronic acid (981 mg, 6.96 mmol). Nitrogen gas was bubbled through the reaction mixture for 10 minutes and  $PdCl_2(dppf)$  (517 mg, 0.633 mmol) was added. The reaction mixture was stirred at 90° C. for 2 hours. After cooling to r.t. it was concentrated to dryness. The residue was purified by silica gel chromatography using 0-100% ethyl acetate in hexanes to afford desired product as brownish oil. LC-MS calculated for  $C_{16}H_{20}ClFN_5OSi$  (M+H)<sup>+</sup>: m/z=380.2; found 380.2.

Step 2. tert-Butyl 3-fluoro-4-(3-(6-fluoropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)benzyl(methyl)carbamate

[0923]



[0924] To a solution of tert-butyl (3-fluoro-5-(trifluoromethyl)benzyl)(methyl)carbamate (Step 1, example 76, 4.50 g, 14.6 mmol) in THF (45.8 ml) was added 2.5M solution of n-butyllithium in hexane (7.03 ml, 17.6 mmol) dropwise at -78° C. over 60 mins. The resulting solution was stirred at -78° C. for 30 mins before 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.48 ml, 22.0 mmol) was added. The reaction mixture was stirred for another 1 hour, allowing it to warm up to r.t. It was acidified to pH=5 by 1N HCl solution. The resulting solution was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over  $MgSO_4$ , filtered and concentrated to dryness. The residue was dissolved in dioxane (20 ml) and water (4 ml) and 5-chloro-3-(6-fluoropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (1.39 g, 3.66 mmol) was added followed by potassium phosphate, tribasic (6.22 g, 29.3 mmol). Nitrogen gas was bubbled through the reaction mixture for 10 minutes. Chloro(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II) (Xphos-Pd-G2, 0.691 g, 0.879 mmol) was added and the reaction mixture was stirred at 60° C. for 1 hour. After cooling to r.t., the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over  $MgSO_4$ , filtered and concentrated to dryness. The residue was purified by silica gel chromatography using 0-100% ethyl acetate in hexanes to afford the desired product as light yellowish oil. LC-MS calculated for  $C_{30}H_{36}F_5N_6O_3Si$  (M+H)<sup>+</sup>: m/z=651.2; found 651.2.

Step 3. (R)-1-(3-Fluoro-4-(3-(6-(2-(methoxymethyl)morpholino)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)phenyl)-N-methylmethanamine

[0925] To a solution of tert-butyl 3-fluoro-4-(3-(6-fluoropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)benzyl(methyl)carbamate (15 mg, 0.024 mmol) in DMSO (1 ml) was added (R)-2-(methoxymethyl)morpholine (31.7 mg,



0.242 mmol) followed by DIPEA (0.021 mL, 0.121 mmol). The resulting mixture was stirred at 120° C. for 15 hours. The reaction mixture was then cooled to r.t., diluted with DCM and washed with water and brine. 1 mL of TFA was added to the separated organic phase and the resulting solution was stirred at 40° C. for 2 hours. It was concentrated to dryness, diluted with methanol and purified using prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min) to afford the desired product. LC-MS calculated for  $C_{25}H_{26}F_4N_7O_2$  (M+H)<sup>+</sup>: m/z=532.2; found 532.2.

#### Example A

##### HPK1 Kinase Binding Assay

**[0926]** A stock solution of 1 mM test compound was prepared in DMSO. The compound plate was prepared by 3-fold and 11-point serial dilutions. 0.1  $\mu$ L of the compound in DMSO was transferred from the compound plate to the white 384 well polystyrene plates. The assay buffer contained 50 mM HEPES, pH 7.5, 0.01% Tween-20, 5 mM  $MgCl_2$ , 0.01% BSA, and 5 mM DTT. 5  $\mu$ L of 4 nM active HPK1 (SignalChem M23-11G) prepared in the buffer was added to the plate. The enzyme concentration given was based on the given stock concentration reported by the vender. 5  $\mu$ L of 18 nM tracer 222 (ThermoFisher PV6121) and 4 nM LanthaScreen Eu-Anti GST antibody (ThermoFisher PV5595) were added. After one hour incubation at 25° C., the plates were read on a PHERAstar FS plate reader (BMG Labtech).  $K_i$  values were determined.

**[0927]** Compounds of the present disclosure, as exemplified in Examples, showed the  $K_i$  values in the following ranges: += $K_i \leq 100$  nM; ++=100 nM< $K_i \leq 500$  nM; +++=500 nM< $K_i \leq 5000$  nM.

TABLE 1

Example	HPK1 $K_i$ , nM
1	+
2	+
3	+
4	+
5	+
6	+
7	+
8	+
9	+
10	+
11	+
12	+
13	++
14	+
15	+
16	++
17	+
18	++
19	+
20	+++
21	+
22	++
23	+
24	+
25	+
26	+
27	+
28	++
29	+
30	+
31	+

TABLE 1-continued

Example	HPK1 $K_i$ , nM
32	+
33	++
34	+
35	+
36	+
37	+
38	+
39	+
40	+
41	+
42	+
43	+
44	+
45	+
46	+
47	++
48	+
49	+
50	+
51	+
52	+
53	+
54	+
55	+
56	+
57	+
58	+
59	+
60	+
61	+
62	+
63	+
64	+
65	+
66	+
67	+
68	+
69	+
70	+
71	+
72	+
73	+
74	+
75	+
76	+
77	+
78	+
79	+
80	+
81	+
82	+
83	+
84	+
85	+
86	+
87	+
88	+
89	+
90	+
91	+
92	+
93	+
94	+
95	+
96	+
97	+
98	+
99	+
100	+
101	+
102	+
103	+
104	+
105	+
106	+

TABLE 1-continued

Example	HPK1 Ki, nM
107	+
108	+
109	+
110	+
111	+
112	+
113	+
114	+
115	+
116	+
117	+
118	+
119	+
120	+
121	+
122	+
123	+
124	+
125	+
126	+

## Example B

## p-SLP76S376 HTRF Assay

**[0928]** One or more compounds of the invention can be tested using the p-SLP76S376 HTRF assay described as follows. Jurkat cells (cultured in RPMI1640 media with 10% FBS) are collected and centrifuged, followed by resuspension in appropriate media at  $3 \times 10^6$  cells/ml. The Jurkat cells (35  $\mu$ l) are dispensed into each well in a 384 well plate. Test compounds are diluted with cell culture media for 40-fold dilution (adding 39  $\mu$ l cell culture media into 1  $\mu$ l compound). The Jurkat cells in the well plate are treated with the test compounds at various concentrations (adding 5  $\mu$ l diluted compound into 35  $\mu$ l Jurkat cells and starting from 3  $\mu$ M with 1:3 dilution) for 1 hour at 37° C., 5% CO<sub>2</sub>, followed by treatment with anti-CD3 (5  $\mu$ g/ml, OKT3 clone) for 30 min. A 1:25 dilution of 100 $\times$  blocking reagent (from p-SLP76 ser376HTRF kit) with 4 $\times$  Lysis Buffer (LB) is prepared and 15  $\mu$ l of the 4 $\times$  LB buffer with blocking reagent is added into each well and incubated at room temperature for 45 mins with gentle shaking. The cell lysate (16  $\mu$ l) is added into a Greiner white plate, treated with p-SLP76 ser376HTRF reagents (2  $\mu$ l donor, 2  $\mu$ l acceptor) and incubated at 4° C. for overnight. The homogeneous time resolved fluorescence (HTRF) is measured on a PHERAstar plate reader the next day. IC<sub>50</sub> determination is performed by fitting the curve of percent inhibition versus the log of the inhibitor concentration using the GraphPad Prism 5.0 software.

## Example C

## Isolation of CD4+ or CD8+ T Cells and Cytokine Measurement

**[0929]** Blood samples are collected from healthy donors. CD4+ or CD8+ T cells are isolated by negative selection using CD4+ or CD8+ enrichment kits (lifetech, USA). The purity of the isolated CD4+ or CD8+ T cells is determined by flow cytometry and is routinely >80%. Cells are cultured in RPMI 1640 supplemented with 10% FCS, glutamine and antibiotics (Invitrogen Life Technologies, USA). For cytokine measurement, Jurkat cells or primary CD4+ or

CD8+ T cells are plated at 200 k cells/well and are stimulated for 24 h with anti-CD3/anti-CD28 beads in the presence or absence of testing compounds at various concentrations. 16  $\mu$ L of supernatants are then transferred to a white detection plate and analyzed using the human IL2 or IFN $\gamma$  assay kits (Cisbio).

## Example D

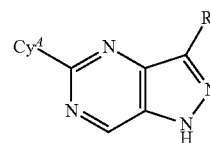
## Treg Assay

**[0930]** One or more compounds can be tested using the Regulatory T-cell proliferation assay described as following. Primary CD4+/CD25- T-cells and CD4+/CD25+ regulatory T-cells are isolated from human donated Peripheral Blood Mononuclear Cells, using an isolated kit from Thermo Fisher Scientific (11363D). CD4+/CD25- T-cells are labeled with CFSE (Thermo Fisher Scientific, C34554) following the protocol provided by the vendor. CFSE labeled T-cells and CD4+/CD25+ regulatory T-cells are re-suspended at the concentration of  $1 \times 10^6$  cells/ml in RPMI-1640 medium. 100  $\mu$ l of CFSE-labeled T-cells are mixed with or without 50  $\mu$ l of CD4+/CD25+ regulatory T-cells, treated with 5  $\mu$ l of anti-CD3/CD28 beads (Thermo Fisher Scientific, 11132D) and various concentrations of compounds diluted in 50  $\mu$ l of RPMI-1640 medium. Mixed populations of cells are cultured for 5 days (37° C., 5% CO<sub>2</sub>) and proliferation of CFSE-labeled T-cells is analyzed by BD LSRFortessa X-20 using FITC channel on the 5th day.

**[0931]** Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including without limitation all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, 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>)R<sup>c</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 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 R<sup>10</sup>; Cy<sup>1</sup> is selected from C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming

heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of the 5-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R<sup>20</sup>;

each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, NO<sub>2</sub>, OR<sup>a1</sup>, SR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, OC(O)R<sup>b1</sup>, OC(O)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(O)R<sup>b1</sup>, NR<sup>c1</sup>C(O)OR<sup>a1</sup>, NR<sup>c1</sup>C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(=NR<sup>e1</sup>)R<sup>b1</sup>, C(=NOR<sup>a1</sup>)R<sup>b1</sup>, C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>S(O)R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>, S(O)R<sup>b1</sup>, S(O)NR<sup>c1</sup>R<sup>d1</sup>, S(O)<sub>2</sub>R<sup>b1</sup>, and S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

or two R<sup>10</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3, ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a3</sup>, SR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>c3</sup>R<sup>d3</sup>, NR<sup>c3</sup>C(O)R<sup>b3</sup>, NR<sup>c3</sup>C(O)OR<sup>a3</sup>, NR<sup>c3</sup>S(O)R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>, S(O)R<sup>b3</sup>, S(O)NR<sup>c3</sup>R<sup>d3</sup>, S(O)<sub>2</sub>R<sup>b3</sup>, and S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,

C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

each R<sup>12</sup> is independently selected from 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>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a5</sup>, SR<sup>a5</sup>, C(O)R<sup>b5</sup>, C(O)NR<sup>c5</sup>R<sup>d5</sup>, C(O)OR<sup>a5</sup>, NR<sup>c5</sup>R<sup>d5</sup>, NR<sup>c5</sup>C(O)R<sup>b5</sup>, NR<sup>c5</sup>C(O)OR<sup>a5</sup>, NR<sup>c5</sup>S(O)R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>, S(O)R<sup>b5</sup>, S(O)NR<sup>c5</sup>R<sup>d5</sup>, S(O)<sub>2</sub>R<sup>b5</sup>, and S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>8</sup>;

each R<sup>20</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, 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>, 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>, C(=NR<sup>e2</sup>)R<sup>b2</sup>, C(=NOR<sup>a2</sup>)R<sup>b2</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>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>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-7</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

each R<sup>21</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a4</sup>, SR<sup>a4</sup>, C(O)R<sup>b4</sup>, C(O)NR<sup>c4</sup>R<sup>d4</sup>, C(O)OR<sup>a4</sup>, NR<sup>c4</sup>R<sup>d4</sup>, NR<sup>c4</sup>C(O)R<sup>b4</sup>, NR<sup>c4</sup>C(O)OR<sup>a4</sup>, NR<sup>c4</sup>S(O)R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>, S(O)R<sup>b4</sup>, S(O)NR<sup>c4</sup>R<sup>d4</sup>, S(O)<sub>2</sub>R<sup>b4</sup>, and S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,

- C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;
- or two R<sup>21</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>22</sup>;
- each R<sup>22</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a6</sup>, SR<sup>a6</sup>, C(O)R<sup>b6</sup>, C(O)NR<sup>c6</sup>R<sup>d6</sup>, C(O)OR<sup>a6</sup>, NR<sup>c6</sup>R<sup>d6</sup>, NR<sup>c6</sup>C(O)R<sup>b6</sup>, NR<sup>c6</sup>C(O)OR<sup>a6</sup>, NR<sup>c6</sup>S(O)R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>, S(O)R<sup>b6</sup>, S(O)NR<sup>c6</sup>R<sup>d6</sup>, S(O)<sub>2</sub>R<sup>b6</sup>, and S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>2</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;
- or any R<sup>c</sup> and R<sup>d</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;
- each R<sup>e</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;
- each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;
- or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;
- each R<sup>e1</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;
- or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;
- each R<sup>e2</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;
- each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;
- or any R<sup>c3</sup> and R<sup>d3</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-,

5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>12</sup>;

each R<sup>b3</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

each R<sup>a4</sup>, R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

or any R<sup>c4</sup> and R<sup>d4</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>22</sup>;

each R<sup>b4</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;

each R<sup>a5</sup>, R<sup>c5</sup> and R<sup>d5</sup> is independently selected from H, 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; 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 R<sup>8</sup>;

each R<sup>b5</sup> is independently selected from 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; 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 R<sup>8</sup>;

each R<sup>a6</sup>, R<sup>c6</sup> and R<sup>d6</sup> is independently selected from H, 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; 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 R<sup>8</sup>;

each R<sup>b6</sup> is independently selected from 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; 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 R<sup>8</sup>; and

each R<sup>8</sup> is 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>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkyl-C1-2 alkylene, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> haloalkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkoxy, HO—C<sub>1-3</sub> alkoxy, HO—C<sub>1-3</sub> alkyl, cyano-C<sub>1-3</sub> alkyl, H<sub>2</sub>N—C<sub>1-3</sub> alkyl, 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)amino-

sulfonyl, 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;

provided that:

- 1) R<sup>1</sup> is other than NH<sub>2</sub>;
- 2) R<sup>1</sup> is other than CH<sub>3</sub>;
- 3) R<sup>1</sup> is other than CH<sub>2</sub>(quinolin-6-yl);
- 4) R<sup>1</sup> is other than NHC(O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; and
- 5) when Cy<sup>d</sup> is unsubstituted or substituted pyrazol-4-yl, then R<sup>1</sup> is other than pyridin-4-yl substituted by morpholine.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>C(O)R<sup>b</sup>, NR<sup>c</sup>C(O)OR<sup>a</sup>, NR<sup>c</sup>S(O)R<sup>b</sup>, NR<sup>c</sup>S(O)<sub>2</sub>R<sup>b</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>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 R<sup>10</sup>.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>, and NR<sup>c</sup>C(O)R<sup>b</sup>; wherein said 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 R<sup>10</sup>.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and OR<sup>a</sup>; wherein said 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 R<sup>10</sup>.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>2-6</sub> alkenyl, and C<sub>2-6</sub> alkynyl; wherein said 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 R<sup>10</sup>.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is Cy<sup>1</sup> or C<sub>2-6</sub> alkenyl; wherein said C<sub>2-6</sub> alkenyl is optionally substituted with 1, 2, or 3 substituents independently selected from R<sup>10</sup>.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is C<sub>2-6</sub> alkenyl; wherein said C<sub>2-6</sub> alkenyl is optionally substituted with 1, 2, or 3 substituents independently selected from R<sup>10</sup>.

8. The compound of claim 7, wherein R<sup>1</sup> is CHCH substituted with R<sup>10</sup>, and R<sup>10</sup> is phenyl substituted with 4-methylpiperazin-1-yl.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is Cy<sup>1</sup>.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Cy<sup>1</sup> is selected from 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl

are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ .

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $Cy^1$  is  $C_{6-10}$  aryl or 5-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ .

12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $Cy^1$  is  $C_{6-10}$  aryl optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ .

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $Cy^1$  is 5-10 membered heteroaryl optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ .

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $Cy^1$  is phenyl, pyrazolyl, pyridinyl, pyrimidinyl, thiophenyl, and pyridone; wherein the phenyl, pyrazolyl, pyridinyl, pyrimidinyl, thiophenyl, or pyridone are each optionally substituted with 1, 2 or 3 substituents independently selected from  $R^{10}$ .

15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $NO_2$ ,  $OR^{a1}$ ,  $SR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $OC(O)R^{b1}$ ,  $OC(O)NR^{c1}R^{d1}$ ,  $NR^{c1}R^{d1}$ ,  $NR^{c1}C(O)R^{b1}$ ,  $NR^{c1}C(O)OR^{a1}$ ,  $NR^{c1}S(O)R^{b1}$ ,  $NR^{c1}S(O)_2R^{b1}$ ,  $S(O)R^{b1}$ ,  $S(O)NR^{c1}R^{d1}$ ,  $S(O)_2R^{b1}$ , and  $S(O)_2NR^{c1}R^{d1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ .

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $NR^{c1}R^{d1}$ ,  $NR^{c1}C(O)R^{b1}$ , and  $S(O)_2R^{b1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ .

17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$

haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $NR^{c1}R^{d1}$ , and  $NR^{c1}C(O)R^{b1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ .

18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $NR^{c1}R^{d1}$ , and  $S(O)_2R^{b1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{11}$ .

19. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ , and  $NR^{c1}R^{d1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{11}$ .

20. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a3}$ ,  $C(O)R^{b3}$ ,  $C(O)NR^{c3}R^{d3}$ ,  $NR^{c3}R^{d3}$ ,  $NR^{c3}C(O)R^{b3}$ ,  $NR^{c3}S(O)_2R^{b3}$ , and  $S(O)_2R^{b3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ .

21. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $OR^{a3}$ ,  $C(O)R^{b3}$ ,  $C(O)NR^{c3}R^{d3}$ ,  $NR^{c3}R^{d3}$ , and  $NR^{c3}C(O)R^{b3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and

5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ .

22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, 4-10 membered heterocycloalkyl, halo, CN,  $OR^{a3}$ ,  $C(O)R^{b3}$ ,  $NR^{c3}R^{d3}$ ,  $C(O)NR^{c3}R^{d3}$ ,  $NR^{c3}C(O)R^{b3}$ ,  $NR^{c3}S(O)_2R^{b3}$ , and  $S(O)_2R^{b3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ .

23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, 4-10 membered heterocycloalkyl, halo, CN,  $C(O)R^{b3}$ ,  $NR^{c3}R^{d3}$ , and  $NR^{c3}C(O)R^{b3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ .

24. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl, 4-10 membered heterocycloalkyl, CN,  $OR^{a3}$ ,  $C(O)R^{b3}$ ,  $NR^{c3}R^{d3}$ ,  $NR^{c3}S(O)_2R^{b3}$ , and  $S(O)_2R^{b3}$ ; wherein said  $C_{1-6}$  alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ .

25. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl, 4-10 membered heterocycloalkyl, CN,  $C(O)R^{b3}$ , and  $NR^{c3}R^{d3}$ ; wherein said  $C_{1-6}$  alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from  $R^{12}$ .

26. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^{a5}$ ,  $SR^{a5}$ ,  $C(O)R^{b5}$ ,  $C(O)NR^{c5}R^{d5}$ ,  $C(O)OR^{a5}$ ,  $NR^{c5}R^{d5}$ , or  $NR^{c5}C(O)R^{b5}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ .

27. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, and  $OR^{a5}$ .

28. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, and halo.

29. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{12}$  is independently  $OR^{a5}$ .

30. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl.

31. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{12}$  is  $C_{1-6}$  alkyl.

32. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  is 4-methylpiperazin-1-yl, fluoro, methyl, CN, trifluoromethyl, methoxy, N,N-dimethylaminocarbonyl, (4-methylpiperazin-1-yl)methyl, 4-morpholinylmethyl, morpholinyl, piperazin-1-yl, pyrrolidin-1-yl, N,N-dimethylamine, morpholinylmethanone,

N-cyclopentylaminocarbonyl, 4-(cycloprop-1-yl)morpholine, cyanomethyl, 4-ethylpiperazin-1-yl, N-methylaminocarbonyl, cyclopropyl, pyridin-1-yl, methylamine, 1-methyl-1-cyanomethyl, tetrahydro-2H-pyran-4-yl, phenyl, 1-(piperazin-1-yl)ethan-1-one, 3-hydroxy-piperidin-1-yl, 4-cyano-piperidin-1-yl, 3-hydroxy-pyrrolidin-1-yl, piperidin-4-yl, 4-(2-methyl-2-hydroxypropyl)piperazin-1-yl, 3-methyl-3(methylhydroxy)piperidin-1-yl, 1-(methylsulfonyl)piperidin-4-amino, 4-(ethylhydroxy)piperazin-1-yl, 4-(methylsulfonyl)piperazin-1-yl, 4-((N-methyl-N-ethyl)aminocarbonyl)piperazin-1-yl, piperidin-1-yl, 4-(methylcarbonyl)piperazin-1-yl, 2-cyanophenyl, 1-hydroxyethane-2-amino, (methylsulfonyl)amino-methyl, azetidin-1-ylsulfonyl, difluoromethoxy, 2-(methoxymethyl)morpholin-4-yl, 4-methyl-4-hydroxypiperidin-1-yl, or 4-(2-methoxyethyl)piperazin-1-yl.

33. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  is 4-methylpiperazin-1-yl, fluoro, methyl, CN, trifluoromethyl, methoxy, N,N-dimethylaminocarbonyl, (4-methylpiperazin-1-yl)methyl, 4-morpholinylmethyl, morpholinyl, piperazin-1-yl, pyrrolidin-1-yl, N,N-dimethylamine, morpholinylmethanone, N-cyclopentylaminocarbonyl, 4-(cycloprop-1-yl)morpholine, cyanomethyl, 4-ethylpiperazin-1-yl, N-methylaminocarbonyl, cyclopropyl, pyridin-1-yl, methylamine, 1-methyl-1-cyanomethyl, tetrahydro-2H-pyran-4-yl, phenyl, or 1-(piperazin-1-yl)ethan-1-one.

34. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $Cy^A$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 6-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{20}$ .

35. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $Cy^A$  is phenyl, pyridinyl, isoindolin-1-onyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolinyl, 2,3-dihydro-1H-inden-5-yl, or 1,2,3,4-tetrahydronaphthyl; wherein the phenyl, pyridinyl, isoindolin-1-onyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolinyl, 2,3-dihydro-1H-inden-5-yl, and 1,2,3,4-tetrahydronaphthyl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{20}$ .

36. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $Cy^A$  is phenyl, pyridinyl, isoindolin-1-onyl, or 1,2,3,4-tetrahydroisoquinolinyl; wherein the phenyl, pyridinyl, isoindolin-1-onyl, and 1,2,3,4-tetrahydroisoquinolinyl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{20}$ .

37. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each  $R^{20}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, 4-10 membered heterocycloalkyl, halo, CN,  $OR^{a2}$ ,  $SR^{a2}$ ,  $C(O)R^{b2}$ ,  $C(O)NR^{c2}R^{d2}$ ,  $C(O)OR^{a2}$ ,  $OC(O)R^{b2}$ ,  $OC(O)NR^{c2}R^{d2}$ ,  $NR^{c2}R^{d2}$ ,  $NR^{c2}C(O)R^{b2}$ ,  $NR^{c2}C(O)OR^{a2}$ ,  $NR^{c2}S(O)_2R^{b2}$ ,  $NR^{c2}S(O)_2R^{b2}$ ,  $S(O)_2R^{b2}$ ,  $S(O)_2NR^{c2}R^{d2}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{21}$ ; or two adjacent  $R^{20}$  substituents on the

Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>.

**38.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>, 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>S(O)R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>R<sup>b2</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>; 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 R<sup>21</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>.

**39.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, 4-10 membered heterocycloalkyl, halo, 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>, NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; 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 R<sup>21</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1 or 2 substituents independently selected from R<sup>21</sup>.

**40.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, 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>, NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; 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 R<sup>21</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring.

**41.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R<sup>20</sup> is independently

selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, 4-10 membered heterocycloalkyl, halo, OR<sup>a2</sup>, C(O)R<sup>b2</sup>, C(O)NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring or a fused C<sub>3-7</sub> cycloalkyl ring; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1 or 2 substituents independently selected from R<sup>21</sup>.

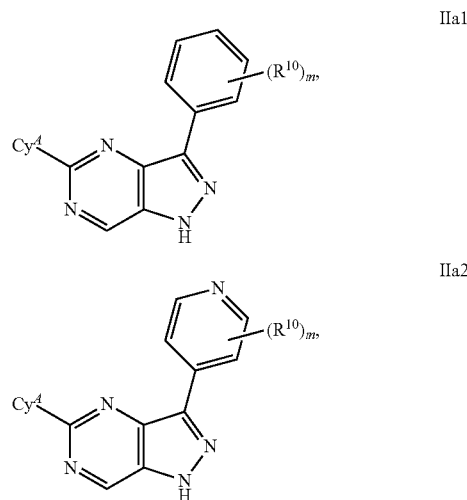
**42.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, halo, OR<sup>a2</sup>, C(O)R<sup>b2</sup>, and C(O)NR<sup>c2</sup>R<sup>d2</sup>; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring.

**43.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>20</sup> is fluoro, methyl, methoxy, chloro, (morpholino)methanone, N-methylaminocarbonyl, aminocarbonyl, (methylamino)methyl, trifluoromethyl, pyrrolidin-2-yl, piperidin-2-yl, ((pyrrolidin-1-yl)methyl)carbonylamino, ((N,N-dimethylamino)methyl)carbonylamino, C(O)H, 1-(methylamino)-ethyl, (ethylamino)methyl, cyanomethyl, N-methylamino, or amino; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused piperidinyl ring.

**44.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>20</sup> is fluoro, methyl, methoxy, chloro, (morpholino)methanone, N-methylaminocarbonyl, or aminocarbonyl; or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused piperidinyl ring.

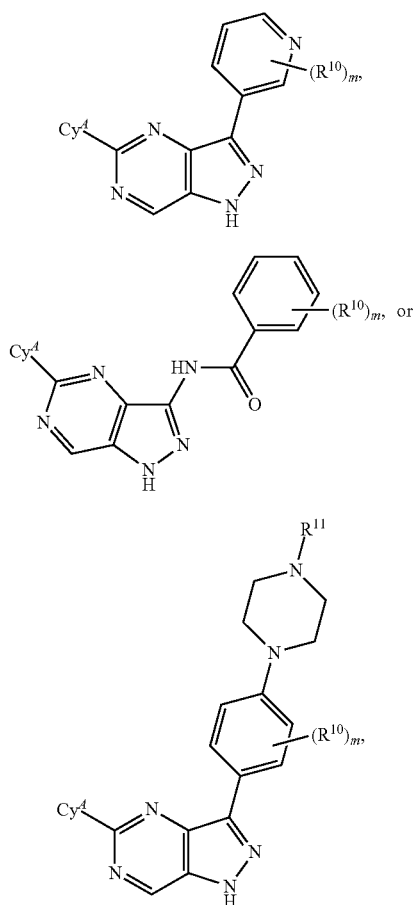
**45.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Cy<sup>4</sup> is 2-fluoro-6-methoxyphenyl.

**46.** The compound of claim 1 having Formula (IIa1), Formula (IIa2), Formula (IIa3), Formula (IIa4) or Formula (IIa5):



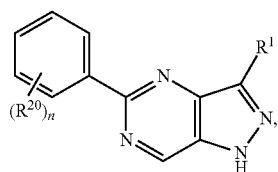


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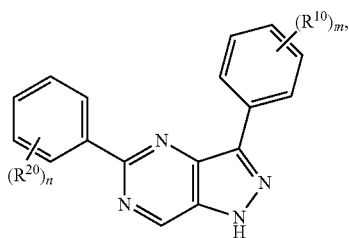
or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4.

47. The compound of claim 1 having Formula (IIb1);

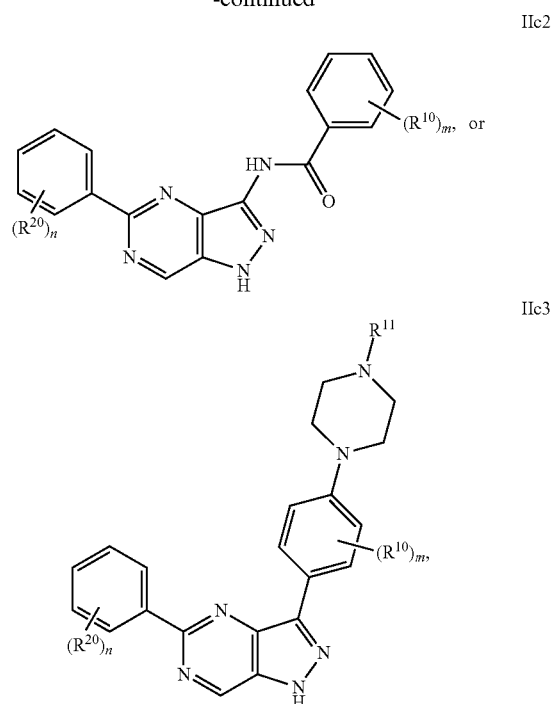


or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, 2, 3, 4 or 5.

48. The compound of claim 1 having Formula (IIc1), Formula (IIc2) or Formula (IIc3):

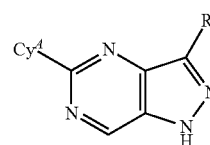


-continued



or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, 3, or 4; and n is 0, 1, 2, 3, 4, or 5.

49. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $NO_2$ ,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cC(O)NR^cR^d$ ,  $C(=NR^e)R^b$ ,  $C(=NOR^a)R^b$ ,  $C(=NR^e)NR^cR^d$ ,  $NR^cC(=NR^e)NR^cR^d$ ,  $NR^cS(O)R^b$ ,  $NR^cS(O)_2R^b$ ,  $NR^cS(O)_2NR^cR^d$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;

$Cy^1$  is selected from  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{3-10}$  cycloalkyl, 4-10 membered hetero-

cycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;

Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 6-10 membered heteroaryl; wherein the 6-10 membered heteroaryl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R<sup>20</sup>;

each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, NO<sub>2</sub>, OR<sup>a1</sup>, SR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, OC(O)R<sup>b1</sup>, OC(O)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(O)R<sup>b1</sup>, NR<sup>c1</sup>C(O)OR<sup>a1</sup>, NR<sup>c1</sup>C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(=NR<sup>e1</sup>)R<sup>b1</sup>, C(=NOR<sup>a1</sup>)R<sup>b1</sup>, C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>C(=NR<sup>e1</sup>)NR<sup>c1</sup>R<sup>d1</sup>, NR<sup>c1</sup>S(O)R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>R<sup>b1</sup>, NR<sup>c1</sup>S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>, S(O)R<sup>b1</sup>, S(O)NR<sup>c1</sup>R<sup>d1</sup>, S(O)<sub>2</sub>R<sup>b1</sup>, and S(O)<sub>2</sub>NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;

or two R<sup>10</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3, ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;

each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a3</sup>, SR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>c3</sup>R<sup>d3</sup>, NR<sup>c3</sup>C(O)R<sup>b3</sup>, NR<sup>c3</sup>C(O)OR<sup>a3</sup>, NR<sup>c3</sup>S(O)R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>R<sup>b3</sup>, NR<sup>c3</sup>S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>, S(O)R<sup>b3</sup>, S(O)NR<sup>c3</sup>R<sup>d3</sup>, S(O)<sub>2</sub>R<sup>b3</sup>, and S(O)<sub>2</sub>NR<sup>c3</sup>R<sup>d3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each

optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;

each R<sup>12</sup> is independently selected from 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>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a5</sup>, SR<sup>a5</sup>, C(O)R<sup>b5</sup>, C(O)NR<sup>c5</sup>R<sup>d5</sup>, C(O)OR<sup>a5</sup>, NR<sup>c5</sup>R<sup>d5</sup>, NR<sup>c5</sup>C(O)R<sup>b5</sup>, NR<sup>c5</sup>C(O)OR<sup>a5</sup>, NR<sup>c5</sup>S(O)R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>R<sup>b5</sup>, NR<sup>c5</sup>S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>, S(O)R<sup>b5</sup>, S(O)NR<sup>c5</sup>R<sup>d5</sup>, S(O)<sub>2</sub>R<sup>b5</sup>, and S(O)<sub>2</sub>NR<sup>c5</sup>R<sup>d5</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>8</sup>;

each R<sup>20</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, 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>, 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>, C(=NR<sup>e2</sup>)R<sup>b2</sup>, C(=NOR<sup>a2</sup>)R<sup>b2</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>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>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;

or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;

each R<sup>21</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a4</sup>, SR<sup>a4</sup>, C(O)R<sup>b4</sup>, C(O)NR<sup>c4</sup>R<sup>d4</sup>, C(O)OR<sup>a4</sup>, NR<sup>c4</sup>R<sup>d4</sup>, NR<sup>c4</sup>C(O)R<sup>b4</sup>, NR<sup>c4</sup>C(O)OR<sup>a4</sup>, NR<sup>c4</sup>S(O)R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>R<sup>b4</sup>, NR<sup>c4</sup>S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>, S(O)R<sup>b4</sup>, S(O)NR<sup>c4</sup>R<sup>d4</sup>, S(O)<sub>2</sub>R<sup>b4</sup>, and S(O)<sub>2</sub>NR<sup>c4</sup>R<sup>d4</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each

- optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>22</sup>;
- or two R<sup>21</sup> substituents taken together with the carbon atom to which they are attached form a spiro 3-7-membered heterocycloalkyl ring, or a spiro C<sub>3-6</sub> cycloalkyl ring; wherein each spiro 3-7-membered heterocycloalkyl ring has at least one ring-forming carbon atom and 1, 2 or 3 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each spiro 3-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 3-7-membered heterocycloalkyl ring and spiro C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>22</sup>;
- each R<sup>22</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, halo, CN, OR<sup>a6</sup>, SR<sup>a6</sup>, C(O)R<sup>b6</sup>, C(O)NR<sup>c6</sup>R<sup>d6</sup>, C(O)OR<sup>a6</sup>, NR<sup>c6</sup>R<sup>d6</sup>, NR<sup>c6</sup>C(O)R<sup>b6</sup>, NR<sup>c6</sup>C(O)OR<sup>a6</sup>, NR<sup>c6</sup>S(O)R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>R<sup>b6</sup>, NR<sup>c6</sup>S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>, S(O)R<sup>b6</sup>, S(O)NR<sup>c6</sup>R<sup>d6</sup>, S(O)<sub>2</sub>R<sup>b6</sup>, and S(O)<sub>2</sub>NR<sup>c6</sup>R<sup>d6</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>g</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;
- or any R<sup>c</sup> and R<sup>d</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;
- each R<sup>b</sup> is independently selected from C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl; wherein said C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;
- each R<sup>e</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;
- each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;
- or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;
- each R<sup>e1</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;
- or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>21</sup>;
- each R<sup>c2</sup> is independently selected from H, CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylaminosulfonyl, carbamyl, C<sub>1-6</sub> alkylcarbamyl, di(C<sub>1-6</sub> alkyl)carbamyl, aminosulfonyl, C<sub>1-6</sub> alkylaminosulfonyl and di(C<sub>1-6</sub> alkyl)aminosulfonyl;
- each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;
- or any R<sup>c3</sup> and R<sup>d3</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from R<sup>12</sup>;
- each R<sup>b3</sup> is independently selected from 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>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl,

- $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ ;
- each  $R^{a4}$ ,  $R^{c4}$  and  $R^{d4}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said  $C_{1-6}$  alkyl  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{22}$ ;
- or any  $R^{c4}$  and  $R^{d4}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 substituents independently selected from  $R^{22}$ ;
- each  $R^{b4}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl; wherein said  $C_{1-6}$  alkyl  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{22}$ ;
- each  $R^{a5}$ ,  $R^{c5}$  and  $R^{d5}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ;
- each  $R^{b5}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ;
- each  $R^{a6}$ ,  $R^{c6}$  and  $R^{d6}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ;
- each  $R^{b6}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^8$ ; and
- each  $R^8$  is independently selected from OH,  $NO_2$ , CN, halo,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-2}$  alkylene,  $C_{1-6}$  alkoxy,  $C_{1-6}$  haloalkoxy,  $C_{1-3}$  alkoxy- $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy- $C_{1-3}$  alkoxy,  $HO-C_{1-3}$  alkoxy,  $HO-C_{1-3}$  alkyl, cyano- $C_{1-3}$  alkyl,  $H_2N-C_{1-3}$  alkyl, amino,  $C_{1-6}$  alkylamino, di( $C_{1-6}$  alkyl)amino, thio,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkylsulfanyl,  $C_{1-6}$  alkylsulfonyl, carbamyl,  $C_{1-6}$  alkylcarbamyl, di( $C_{1-6}$  alkyl)carbamyl, carboxy,  $C_{1-6}$  alkylcarbonyl,  $C_{1-6}$  alkoxycarbonyl,  $C_{1-6}$  alkylcarbonylamino,  $C_{1-6}$  alkylsulfonylamino, amino-sulfonyl,  $C_{1-6}$  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.
50. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- $R^1$  is selected from  $Cy^1$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^a$ ,  $SR^a$ ,  $C(O)R^b$ ,  $C(O)NR^cR^d$ ,  $C(O)OR^a$ ,  $OC(O)R^b$ ,  $OC(O)NR^cR^d$ ,  $NR^cC(O)R^b$ ,  $NR^cC(O)OR^a$ ,  $NR^cS(O)R^b$ ,  $NR^cS(O)_2R^b$ ,  $S(O)R^b$ ,  $S(O)NR^cR^d$ ,  $S(O)_2R^b$ , and  $S(O)_2NR^cR^d$ ; wherein said  $C_{2-6}$  alkenyl and  $C_{2-6}$  alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{10}$ ;
- $Cy^1$  is selected from 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{10}$ ;
- $Cy^4$  is selected from  $C_{6-10}$  aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the  $C_{6-10}$  aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from  $R^{20}$ ;
- each  $R^{10}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene, 5-10 membered heteroaryl- $C_{1-3}$  alkylene, halo, CN,  $NO_2$ ,  $OR^{a1}$ ,  $SR^{a1}$ ,  $C(O)R^{b1}$ ,  $C(O)NR^{c1}R^{d1}$ ,  $C(O)OR^{a1}$ ,  $OC(O)R^{b1}$ ,  $OC(O)NR^{c1}R^{d1}$ ,  $NR^{c1}R^{d1}$ ,  $NR^{c1}C(O)R^{b1}$ ,  $NR^{c1}C(O)OR^{a1}$ ,  $NR^{c1}S(O)R^{b1}$ ,  $NR^{c1}S(O)_2R^{b1}$ ,  $S(O)R^{b1}$ ,  $S(O)NR^{c1}R^{d1}$ ,  $S(O)_2R^{b1}$ , and  $S(O)_2NR^{c1}R^{d1}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl,  $C_{3-10}$  cycloalkyl- $C_{1-3}$  alkylene, 4-10 membered heterocycloalkyl- $C_{1-3}$  alkylene,  $C_{6-10}$  aryl- $C_{1-3}$  alkylene and 5-10 membered heteroaryl- $C_{1-3}$  alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{11}$ ;
- each  $R^{11}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, 5-10 membered heteroaryl, halo, CN,  $OR^{a3}$ ,  $SR^{a3}$ ,  $C(O)R^{b3}$ ,  $C(O)NR^{c3}R^{d3}$ ,  $C(O)OR^{a3}$ ,  $NR^{c3}R^{d3}$ ,  $NR^{c3}S(O)R^{b3}$ , and  $NR^{c3}C(O)OR^{a3}$ ; wherein said  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl, 4-10 membered heterocycloalkyl,  $C_{6-10}$  aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from  $R^{12}$ ;
- each  $R^{12}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo,  $OR^{a5}$ ,  $SR^{a5}$ ,  $C(O)R^{b5}$ ,  $C(O)NR^{c5}R^{d5}$ ,  $C(O)OR^{a5}$ ,  $NR^{c5}R^{d5}$ ,  $NR^{c5}C(O)OR^{a5}$ ; and  $NR^{c5}C(O)OR^{a5}$ ;
- each  $R^{20}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, CN,  $OR^{a2}$ ,

- 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>, 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>S(O)R<sup>b2</sup>, NR<sup>c2</sup>S(O)<sub>2</sub>R<sup>b2</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>; 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 R<sup>21</sup>;
- or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;
- each R<sup>21</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, OR<sup>a4</sup>, SR<sup>a4</sup>, C(O)R<sup>b4</sup>, C(O)NR<sup>c4</sup>R<sup>d4</sup>, C(O)OR<sup>a4</sup>, NR<sup>c4</sup>R<sup>d4</sup>, NR<sup>c4</sup>C(O)R<sup>b4</sup>, and NR<sup>c4</sup>C(O)OR<sup>a4</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered hetero cycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;
- each R<sup>b</sup> is independently selected from C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl; wherein said C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;
- each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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>3-10</sub> cycloalkyl, 4-10 membered hetero cycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;
- or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl;
- 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, and C<sub>1-6</sub> haloalkyl;
- or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl;
- each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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;
- each R<sup>b3</sup> is independently selected from 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;
- each R<sup>a4</sup>, R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H, 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;
- each R<sup>b4</sup> is independently selected from 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;
- each R<sup>a5</sup>, R<sup>c5</sup> and R<sup>d5</sup> is independently selected from H, 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; and
- each R<sup>b5</sup> is independently selected from 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.
- 51.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- R<sup>1</sup> is selected from Cy<sup>1</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, 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>, and NR<sup>c</sup>C(O)R<sup>b</sup>; wherein said 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 R<sup>10</sup>;
- Cy<sup>1</sup> is selected from 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered hetero aryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;
- Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or substituents independently selected from R<sup>20</sup>;
- each R<sup>10</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene, 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, C(O)OR<sup>a1</sup>, NR<sup>c1</sup>R<sup>d1</sup>, and NR<sup>c1</sup>C(O)R<sup>b1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, C<sub>3-10</sub> cycloalkyl-C<sub>1-3</sub> alkylene,

- 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, C<sub>6-10</sub> aryl-C<sub>1-3</sub> alkylene and 5-10 membered heteroaryl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;
- each R<sup>11</sup> is independently selected from 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>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, halo, CN, OR<sup>a3</sup>, C(O)R<sup>b3</sup>, C(O)NR<sup>c3</sup>R<sup>d3</sup>, C(O)OR<sup>a3</sup>, NR<sup>c3</sup>R<sup>d3</sup>, and NR<sup>c3</sup>C(O)R<sup>b3</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;
- each R<sup>12</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, and halo;
- each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, CN, OR<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>, NR<sup>c2</sup>R<sup>d2</sup>, and NR<sup>c2</sup>C(O)R<sup>b2</sup>; 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 R<sup>21</sup>;
- or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring, or a fused C<sub>3-7</sub> cycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring and fused C<sub>3-6</sub> cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;
- each R<sup>21</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, halo, and NR<sup>c4</sup>R<sup>d4</sup>;
- 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, and C<sub>1-6</sub> haloalkyl; 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 R<sup>10</sup>;
- each R<sup>b</sup> is independently selected from C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, and C<sub>1-6</sub> haloalkyl;
- each R<sup>a1</sup>, R<sup>c1</sup> and R<sup>d1</sup> is independently selected from H, 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;
- or any R<sup>c1</sup> and R<sup>d1</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>11</sup>;
- 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, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, and 4-10 membered heterocycloalkyl;
- 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, and C<sub>1-6</sub> haloalkyl;
- or any R<sup>c2</sup> and R<sup>d2</sup> attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>21</sup>;
- 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, C<sub>1-6</sub> haloalkyl, and 4-10 membered heterocycloalkyl;
- each R<sup>a3</sup>, R<sup>c3</sup> and R<sup>d3</sup> is independently selected from H, 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;
- each R<sup>b3</sup> is independently selected from 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; and
- each R<sup>c4</sup> and R<sup>d4</sup> is independently selected from H and C<sub>1-6</sub> alkyl.
- 52.** The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- R<sup>1</sup> is selected from Cy<sup>1</sup> and C<sub>2-6</sub> alkenyl; wherein said C<sub>2-6</sub> alkenyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>10</sup>;
- Cy<sup>1</sup> is selected from 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl; wherein the 4-10 membered heterocycloalkyl and 5-10 membered heteroaryl each has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R<sup>10</sup>;
- Cy<sup>4</sup> is selected from C<sub>6-10</sub> aryl and 6-10 membered heteroaryl; wherein the 5-10 membered heteroaryl has at least one ring-forming carbon atom and 1 or 2 ring-forming N heteroatoms; wherein a ring-forming carbon atom of the 6-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C<sub>6-10</sub> aryl and 6-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>20</sup>;
- each R<sup>10</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene, halo, CN, OR<sup>a1</sup>, C(O)R<sup>b1</sup>, C(O)NR<sup>c1</sup>R<sup>d1</sup>, and NR<sup>c1</sup>R<sup>d1</sup>; wherein said C<sub>1-6</sub> alkyl, C<sub>3-10</sub> cycloalkyl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl, and 4-10 membered heterocycloalkyl-C<sub>1-3</sub> alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>11</sup>;
- each R<sup>11</sup> is independently selected from C<sub>1-6</sub> alkyl, 4-10 membered heterocycloalkyl, CN, C(O)R<sup>d3</sup>, and NR<sup>c3</sup>R<sup>d3</sup>; wherein said C<sub>1-6</sub> alkyl and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R<sup>12</sup>;
- each R<sup>12</sup> is independently C<sub>1-6</sub> alkyl;
- each R<sup>20</sup> is independently selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, halo, COR<sup>a2</sup>, C(O)R<sup>b2</sup>, and C(O)NR<sup>c2</sup>R<sup>d2</sup>; wherein said C<sub>1-6</sub> alkyl is optionally substituted with 1, 2, or 3, substituents independently selected from R<sup>21</sup>;
- or two adjacent R<sup>20</sup> substituents on the Cy<sup>4</sup> ring, taken together with the atoms to which they are attached, form a fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring; wherein the fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring each has at least one ring-forming

carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, O, and S; wherein a ring-forming carbon atom of each fused 4-, 5-, 6- or 7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group;

each  $R^{21}$  is independently selected from  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  haloalkyl, halo, and  $NR^{c4}R^{d4}$ ;

each  $R^{a1}$ ,  $R^{c1}$  and  $R^{d1}$  is independently selected from H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, and  $C_{1-6}$  haloalkyl;

or any  $R^{c1}$  and  $R^{d1}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from  $R^{11}$ ;

each  $R^{b1}$  is independently  $C_{3-10}$  cycloalkyl or 4-10 membered heterocycloalkyl;

each  $R^{a2}$ ,  $R^{c2}$  and  $R^{d2}$  is independently selected from H and  $C_{1-6}$  alkyl;

or any  $R^{c2}$  and  $R^{d2}$  attached to the same N atom, together with the N atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

each  $R^{b2}$  is independently 4-10 membered heterocycloalkyl;

each  $R^{c3}$  and  $R^{d3}$  is H;

each  $R^{b3}$  is  $C_{1-6}$  alkyl; and

each  $R^{c4}$  and  $R^{d4}$  is independently selected from H and  $C_{1-6}$  alkyl.

**53.** The compound of claim 1 selected from:

5-(2-Fluorophenyl)-3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazolo[4,3-d]pyrimidine,

3-(4-(4-Methylpiperazin-1-yl)phenyl)-5-o-tolyl-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Chloro-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

3-(4-(4-Methylpiperazin-1-yl)phenyl)-5-(pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine,

3-(4-(4-Methylpiperazin-1-yl)phenyl)-5-(5-methylpyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine,

6-(3-(4-(4-Methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)isoindolin-1-one,

(5-(3-(4-(4-Methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-3-yl)(morpholino) methanone,

N-Methyl-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)nicotinamide,

5-(3-(4-(4-Methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline,

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-phenyl-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(2-fluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidine,

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzonitrile,

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(3-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-o-tolyl-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(thiophen-3-yl)-1H-pyrazolo[4,3-d]pyrimidine,

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N,N-dimethylbenzamide,

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

4-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzyl)morpholine

5-(2-Fluoro-6-methoxyphenyl)-3-(3-(4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

4-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)morpholine,

5-(2-Fluoro-6-methoxyphenyl)-3-(3-(piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-fluoro-6-methoxyphenyl)-3-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

4-(3-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)morpholine,

3-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N,N-dimethylaniline,

(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)(morpholino)methanone,

N-Cyclopentyl-4-(5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzamide,

4-(1-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)cyclopropyl)morpholine,

2-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)phenylacetone nitrile,

5-(2-Fluoro-6-methoxyphenyl)-3-(4-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(4-fluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine,

3-(4-(4-Ethylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine,

4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N-methylbenzamide,

3-(4-Cyclopropylphenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(piperidin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)methanamine,

2-(4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)-2-methylpropanenitrile,

5-(2-Fluoro-6-methoxyphenyl)-3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2,3-Difluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

5-(2,3-Difluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine,

2-Fluoro-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzamide,

2-Fluoro-N-methyl-3-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzamide,

- 5-(2-Fluoro-6-methoxyphenyl)-3-(1-phenyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidine,  
 4-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1-methylpyridin-2(1H)-one,  
 5-(2-Fluoro-6-methoxyphenyl)-3-(2-(piperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine,  
 5-(2-Fluoro-6-methoxyphenyl)-3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine,  
 5-(2-Fluoro-6-methoxyphenyl)-3-(6-(piperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine,  
 4-(5-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)morpholine,  
 1-(4-(5-(5-(2-Fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)piperazin-1-yl)ethan-1-one,  
 (E)-5-(2-Fluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)styryl)-1H-pyrazolo[4,3-d]pyrimidine, and  
 6-Fluoro-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline,  
 or a pharmaceutically acceptable salt thereof.
- 54.** The compound of claim 1 selected from:
- 1-(4-(5-(2-Fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperidin-3-ol;  
 1-(4-(5-(2-Fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperidine-4-carbonitrile;  
 5-(2-Fluoro-6-methylphenyl)-3-(4-(piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine;  
 1-(4-(5-(2-Fluoro-6-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)pyrrolidin-3-ol;  
 5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N-methylpicolinamide;  
 4-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-fluoro-N-methylbenzamide;  
 1-(3,5-Difluoro-4-(3-(4-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 3-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzoxonitrile;  
 1-(3,5-Difluoro-4-(3-(4-(piperidin-4-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 1-(3,5-Difluoro-4-(3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 1-(4-(3-(4-(4-Ethylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-difluorophenyl)-N-methylmethanamine;  
 5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-morpholinonitrocinonitrile;  
 1-(3,5-Difluoro-4-(3-(3-fluoro-2-morpholinopyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 1-(4-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)piperazin-1-yl)-2-methylpropan-2-ol;  
 1-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-3-methylpiperidin-3-yl)methanol;  
 N-(4-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)-1-(methylsulfonyl)piperidin-4-amine;  
 2-(4-(4-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperazin-1-yl)ethanol;  
 1-(3,5-Difluoro-4-(3-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 4-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-N-ethyl-N-methylpiperazine-1-carboxamide;  
 1-(3-Fluoro-4-(3-(6-(piperidin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)phenyl)-N-methylmethanamine;  
 1-(4-(5-(5-(2-Fluoro-4-((methylamino)methyl)-6-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)piperazin-1-yl)ethanone;  
 1-(3-Fluoro-5-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 2-(4-(5-(2-Fluoro-6-methyl-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzoxonitrile;  
 5-(2-Fluoro-6-methyl-4-(pyrrolidin-2-yl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine;  
 5-(2-Fluoro-6-methyl-4-(piperidin-2-yl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine;  
 N-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-yl)phenyl)-2-(pyrrolidin-1-yl)acetamide;  
 N-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-yl)phenyl)-2-(dimethylamino)acetamide;  
 1-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 1-(3,5-Difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 1-(3-Fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;  
 N-(3-Fluoro-5-methoxy-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzyl)ethanamine;  
 5-(2-Fluoro-6-methoxyphenyl)-3-(3-methyl-1H-pyrazol-5-yl)-1H-pyrazolo[4,3-d]pyrimidine;  
 3-(Benzyloxy)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-d]pyrimidine;  
 6,8-Difluoro-7-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;  
 2-(5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyrimidin-2-ylamino)ethanol;  
 6,8-Difluoro-7-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;  
 5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N,N-dimethylpyrimidin-2-amine;  
 5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-N-methylpyrimidin-2-amine;



- N-(4-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)benzyl)methanesulfonamide;
- 7-(3-(4-(Azetidin-1-ylsulfonyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-1,2,3,4-tetrahydroisoquinoline;
- 7-(3-(6-(Difluoromethoxy)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-6,8-difluoro-1,2,3,4-tetrahydroisoquinoline;
- 4-(5-(5-(6,8-Difluoro-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)morpholine;
- 6,8-Difluoro-7-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;
- 8-Methoxy-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;
- 8-Fluoro-7-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)quinoline;
- 5-(4-Methoxypyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine;
- 5-(4-Methoxypyridin-3-yl)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine;
- N-Methyl-1-(4-methyl-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-2-yl)methanamine;
- 2-(3,5-Difluoro-4-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)acetonitrile;
- 6-Fluoro-5-(3-(4-(4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;
- 6-Fluoro-8-methyl-7-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;
- 1-(4-(4-(5-(6-Fluoro-8-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperazin-1-yl)ethanone;
- 4-(5-(5-(6-Fluoro-8-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)morpholine;
- 6-Fluoro-8-methyl-7-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;
- 6-Fluoro-8-methyl-7-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;
- 8-Fluoro-6-methyl-7-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline;
- 4,6-Difluoro-N-methyl-5-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine;
- 4,6-Difluoro-N-methyl-5-(3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine;
- 6,8-Difluoro-N-methyl-7-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-2-amine;
- 5,7-Difluoro-N-methyl-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine;
- 5,7-Difluoro-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine;
- 5,7-Difluoro-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine;
- 5-Fluoro-7-methoxy-6-(3-(6-morpholinopyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-amine;
- 6-Fluoro-N-methyl-5-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine;
- 6-Fluoro-5-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-1-amine;
- 1-(5-(5-(2,6-Difluoro-4-((methylamino)methyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-4-methylpiperidin-4-ol;
- 1-(3,5-Difluoro-4-(3-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)-N-methylmethanamine;
- 1-(4-(3-(4-(4-Ethylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-fluoro-5-(trifluoromethyl)phenyl)-N-methylmethanamine;
- 3-(4-(4-Ethylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methyl-4-(piperidin-2-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine; and
- (R)-1-(3-Fluoro-4-(3-(6-(2-(methoxymethyl)morpholino)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-(trifluoromethyl)phenyl)-N-methylmethanamine;
- or a pharmaceutically acceptable salt thereof.
- 55.** A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.
- 56.** A method of inhibiting HPK1 activity, said method comprising administering to a patient a compound of claim 1, or a pharmaceutically acceptable salt thereof.
- 57.** A method of treating a disease or disorder associated with inhibition of HPK1 interaction, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.
- 58.** A method for treating a cancer in a patient, said method comprising: administering to the patient a therapeutically effective amount of the compound of claim 1, or a pharmaceutically acceptable salt thereof.
- 59.** The method of claim 58, wherein the cancer is selected from breast cancer, colorectal cancer, lung cancer, ovarian cancer, and pancreatic cancer.

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