

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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

02 April 2020 (02.04.2020)



(10) International Publication Number

WO 2020/068729 A1

(51) International Patent Classification:

A61P 35/00 (2006.01) A61K 31/519 (2006.01)

C07D 487/04 (2006.01)

(21) International Application Number:

PCT/US2019/052567

(22) International Filing Date:

24 September 2019 (24.09.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/736,121 25 September 2018 (25.09.2018) US

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

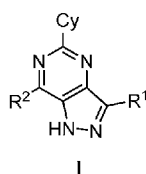
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

— with sequence listing part of description (Rule 5.2(a))

(54) Title: PYRAZOLO[4,3-D]PYRIMIDINE COMPOUNDS AS ALK2 ABD/OR FGFR MODULATORS



(57) Abstract: Disclosed are compounds of Formula (I), methods of using the compounds for inhibiting ALK2 activity and/or FGFR activity, and pharmaceutical compositions comprising such compounds. The compounds are useful in treating, preventing or ameliorating diseases or disorders associated with ALK2 activity and/or FGFR activity, such as cancer.



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PYRAZOLO[4,3-D]PYRIMIDINE COMPOUNDS AS ALK2 AND/OR FGFR MODULATORS

FIELD OF THE INVENTION

5 The disclosure provides compounds as well as their compositions and methods of use. The compounds modulate activin receptor-like kinase-2 (ALK2) activity and/or Fibroblast Growth Factor Receptors (FGFR) activity and are useful in the treatment of various diseases associated with ALK2 and/or FGFR activity including cancer.

BACKGROUND OF THE INVENTION

10 Bone morphogenetic protein (BMP) signaling belongs to the transforming growth factor beta (TGF- β) superfamily and TGF- β signaling ligands include more than 25 different ligands: TGF- β growth and differentiation factors, BMPs and Activins. The binding of BMP ligands leads to the assembly of tetrameric receptor complexes composed of two
15 constitutively-active type II receptor serine/threonine kinases (BMPRII, ACTRIIA, or ACTRIIB) and activate two type I receptor serine/threonine kinases (ALK1, ALK2, ALK3, or ALK6). Furthermore, the activated type I receptors phosphorylate BMP receptor responsive SMAD proteins 1/5/8 and the activated SMAD1/5/8 associated with co-SMAD4 translocate to the nucleus to regulate gene transcription. (Ross, S.L., et al. Cell Metabolism
20 2012, 15, 905-917; Blobe, G.C., et al. New England Journal of Medicine 2000, 342, 1350-1358).

 BMPR kinase activin A receptor, type I (ACVR1) is also called activin receptor-like kinase-2 (ALK2), which is composed of a ligand-binding extracellular domain and a cytoplasmic domain with serine/threonine specificity. ALK2 has been reported to mediate
25 multiple human diseases (Massague, J., et al. Cell 2000, 103, 295-309; Taylor, K.R., et al. Cancer Research 2014, 74, 4565-4570). ALK2 and ALK3 have been shown to play an essential role in regulating the hepcidin levels and affecting the anemia of chronic disease (Andriopoulos, B., et al. Nature Genetics 2009, 41, 482-487; Steinbicker, A.U., et al. Blood
2011, 118, 4224-4230; Steinbicker, A.U., et al. Blood 2011, 117, 4915-4923). Hepcidin is a
30 small peptide hormone primarily synthesized in hepatocytes and reduces both duodenal iron absorption and iron export from monocytes/macrophages by binding to and inducing the internalization and degradation of the iron exporter ferroportin (FPN1) (Theurl, I. et al. Haematologica 2011, 96, 1761-1769; Zhao, N. et al. Journal of Clinical Investigation 2013, 123, 2337-2343). The elevated serum hepcidin levels enhance storage of iron within the

reticuloendothelial system and result in reduced iron availability and iron restricted erythropoiesis. Inappropriately increased hepcidin expression causes severe functional iron deficiency anemia in humans and is central to the pathophysiology of anemia of chronic disease (ACD) (Weiss, G. et al. New England Journal of Medicine 2005, 352, 1011-1023).

5 The Fibroblast Growth Factor Receptors (FGFR) are receptor tyrosine kinases that bind to fibroblast growth factor (FGF) ligands. There are four FGFR proteins (FGFR1-4) that are capable of binding ligands and are involved in the regulation of many physiological processes including tissue development, angiogenesis, wound healing, and metabolic regulation. Upon ligand binding, the receptors undergo dimerization and phosphorylation
10 leading to stimulation of the protein kinase activity and recruitment of many intracellular docking proteins. These interactions facilitate the activation of an array of intracellular signaling pathways including Ras-MAPK, AKT-PI3K, and phospholipase C that are important for cellular growth, proliferation and survival (Reviewed in Eswarakumar et al. Cytokine & Growth Factor Reviews, 2005).

15 Aberrant activation of this pathway either through overexpression of FGF ligands or FGFR or activating mutations in the FGFRs can lead to tumor development, progression, and resistance to conventional cancer therapies. In human cancer, genetic alterations including gene amplification, chromosomal translocations and somatic mutations that lead to ligand-independent receptor activation have been described. Large scale DNA sequencing of
20 thousands of tumor samples has revealed that components of the FGFR pathway are among the most frequently mutated in human cancer. Many of these activating mutations are identical to germline mutations that lead to skeletal dysplasia syndromes. Mechanisms that lead to aberrant ligand-dependent signaling in human disease include overexpression of FGFs and changes in FGFR splicing that lead to receptors with more promiscuous ligand binding
25 abilities (Reviewed in Knights and Cook Pharmacology & Therapeutics, 2010; Turner and Grose, Nature Reviews Cancer, 2010). Therefore, development of inhibitors targeting FGFR may be useful in the clinical treatment of diseases that have elevated FGF or FGFR activity.

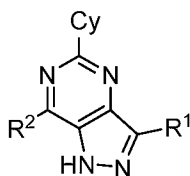
 The cancer types in which FGF/FGFRs are implicated include, but are not limited to: carcinomas (e.g., bladder, breast, cervical, colorectal, endometrial, gastric, head and neck,
30 kidney, liver, lung, ovarian, prostate); hematopoietic malignancies (e.g., multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, acute myelogenous leukemia, non-Hodgkin lymphoma, myeloproliferative neoplasms, and Waldenstrom's Macroglobulinemia); and other neoplasms (e.g., glioblastoma, melanoma, and rhabdosarcoma). In addition to a role in oncogenic neoplasms, FGFR activation has also been implicated in skeletal and

chondrocyte disorders including, but not limited to, achondroplasia and craniosynostosis syndromes.

Accordingly, there is a need for new compounds that modulate ALK2 activity and/or FGFR activity and for compounds capable of treating diseases that are related to ALK2 activity and/or FGFR activity.

SUMMARY

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



I

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

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

The present disclosure further provides methods of inhibiting ALK2 activity, which comprises administering to an individual a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

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

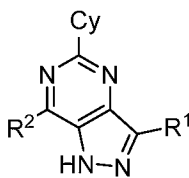
The present disclosure further provides methods of treating a disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds of the present disclosure are inhibitors of ALK2 and/or FGFR activity. In some embodiments, the compounds of the present disclosure are dual ALK2/FGFR inhibitors.

DETAILED DESCRIPTION

Compounds

The present disclosure provides, a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from Cy¹, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=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 C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each substituted with 1, 2, 3, or 4 substituents independently selected from R¹⁰;

Cy¹ is selected from C₃₋₁₄ cycloalkyl, 4-14 membered heterocycloalkyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl; wherein the 4-14 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 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the C₃₋₁₄ cycloalkyl, 4-14 membered heterocycloalkyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R¹⁰;

Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl 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 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-14 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-14 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-14 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰;

R² is selected from H, D, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy and C₁₋₄ haloalkoxy;

each R¹⁰ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋

10 aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, NO₂, 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}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NOR^{a1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1},
 5 S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹¹;

10 or two R¹⁰ substituents taken together with the carbon atom to which they are attached form a spiro 4-7-membered heterocycloalkyl ring, or a spiro C₃₋₆ cycloalkyl ring; wherein each spiro 4-7-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 4-7-membered heterocycloalkyl ring is optionally
 15 substituted by oxo to form a carbonyl group; and wherein the spiro 4-7-membered heterocycloalkyl ring and spiro C₃₋₆ cycloalkyl ring are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered
 20 heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, 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}, NR^{c3}C(O)OR^{a3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered
 25 heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹²;

each R¹² is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆
 30 haloalkyl, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, 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}, NR^{c5}C(O)OR^{a5}, NR^{c5}S(O)R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5};

wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R⁸;

each R²⁰ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, NO₂, 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}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NOR^{a2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

each R²¹ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, 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}, NR^{c4}C(O)OR^{a4}, NR^{c4}S(O)R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, and S(O)₂NR^{c4}R^{d4}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²²;

each R²² is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, OR^{a6}, SR^{a6}, C(O)R^{b6}, C(O)NR^{c6}R^{d6}, C(O)OR^{a6}, NR^{c6}R^{d6}, NR^{c6}C(O)R^{b6}, NR^{c6}C(O)OR^{a6}, NR^{c6}S(O)R^{b6}, NR^{c6}S(O)₂R^{b6}, NR^{c6}S(O)₂NR^{c6}R^{d6}, S(O)R^{b6}, S(O)NR^{c6}R^{d6}, S(O)₂R^{b6}, and S(O)₂NR^{c6}R^{d6};

wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^e;

each R^a, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹⁰;

or any R^c and R^d 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 R¹⁰;

each R^b is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹⁰;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆ alkyl)aminosulfonyl;

each R^{a1}, R^{c1} and R^{d1} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered

heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹¹;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R¹¹;

each R^{b1} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹¹;

each R^{e1} is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆ alkyl)aminosulfonyl;

each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R²¹;

each R^{b2} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆

6 alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

5 each R^{e2} is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆ alkyl)aminosulfonyl;

10 each R^{a3}, R^{c3} and R^{d3} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, 15 phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹²;

or any R^{c3} and R^{d3} 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 R¹²;

20 each R^{b3} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, 25 phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹²;

each R^{a4}, R^{c4} and R^{d4} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, 30 phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene,

phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²²;

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 R²²;

each R^{b4} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²²;

each R^{a5}, R^{c5} and R^{d5} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

or any R^{c5} and R^{d5} 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^g;

each R^{b5} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

each R^{a6}, R^{c6} and R^{d6} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

or any R^{c6} and R^{d6} 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^g;

each R^{b6} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₂ alkylene, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₃ alkoxy-C₁₋₃ alkoxy, HO-C₁₋₃ alkoxy, HO-C₁₋₃ alkyl,

cyano-C₁₋₃ alkyl, H₂N-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, 5 aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

In some embodiments, R¹ is selected from Cy¹, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, 10 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 C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, R¹ is selected from Cy¹, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, 15 OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, and NR^cC(O)OR^a; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, R¹ is selected from Cy¹, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halo, CN, OR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, NR^cR^d, and NR^cC(O)R^b; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each substituted with 1 20 or 2 substituents independently selected from R¹⁰.

In some embodiments, R¹ is selected from Cy¹, C₁₋₆ haloalkyl, halo, CN, OR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, NR^cR^d, and NR^cC(O)R^b.

In some embodiments, R¹ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halo, CN, OR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, NR^cR^d, and 25 NR^cC(O)R^b; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, R¹ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each substituted with 1 or 2 substituents independently selected from R¹⁰.

30 In some embodiments, R¹ is Cy¹.

In some embodiments, Cy¹ is C₃₋₁₄ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is C₃₋₁₂ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is C₄₋₁₀ cycloalkyl optionally substituted with 1 or 2 substituents

independently selected from R¹⁰. In some embodiments, Cy¹ is C₃₋₁₀ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is C₄₋₈ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is C₅₋₆ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is 4-14 membered heterocycloalkyl having 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 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-14 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is 4-12 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl having 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 4-12 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-14 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is selected from C₆₋₁₀ 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 5-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2 or 3 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is selected from C₆₋₁₀ 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 5-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is C₆₋₁₀ aryl optionally substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is phenyl optionally

substituted with 1 or 2 substituents independently selected from R¹⁰. In some embodiments, Cy¹ is phenyl optionally substituted with 1 R¹⁰.

In some embodiments, Cy¹ is 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 5-10 membered heteroaryl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is 5-6 membered heteroaryl; wherein the 5-6 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 5-6 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the 5-6 membered heteroaryl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is phenyl or 5-6 membered heteroaryl; wherein the 5-6 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 5-6 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the phenyl or 5-6 membered heteroaryl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is pyridinyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is pyrazolyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is pyrazolyl, phenyl or pyridinyl, wherein the pyrazolyl, phenyl and pyridinyl are each optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is phenyl or pyridinyl, wherein the phenyl and pyridinyl are each optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, Cy¹ is phenyl, wherein the phenyl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

In some embodiments, R¹⁰ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered

heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, and NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, CN, OR^{a1}, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, and C(O)NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene, are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, CN, and OR^{a1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halo, D, CN, and OR^{a1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is selected from C₁₋₆ alkyl, halo, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, and C(O)NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is selected from C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl; wherein said C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is C₃₋₁₀ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is C₃₋₆ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is cyclohexyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is cyclobutyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is cyclopropyl optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is 4-10 membered heterocycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is 5-6 membered heterocycloalkyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is piperazinyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is pyrrolidinyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is piperidinyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is tetrahydropyranyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is morpholino optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is C₆₋₁₀ aryl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is phenyl optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is 5-10 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is pyridyl optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is imidazo[1,2-a]pyridyl optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R¹⁰ is C₁₋₆ alkyl, optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is methyl, optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is ethyl, optionally substituted with 1 or 2 substituents independently selected from R¹¹. In some embodiments, R¹⁰ is isopropyl, optionally substituted with 1 or 2 substituents independently selected from R¹¹.

In some embodiments, R^{10} is $C(O)NR^{c1}R^d$. In some embodiments, each R^{c1} and R^d is independently selected from H, and C_{1-6} alkyl. In some embodiments, R^{10} is methylcarbamoyl.

In some embodiments, R^{10} is 4-10 membered heterocycloalkyl- C_{1-3} alkylene optionally substituted with 1 or 2 substituents independently selected from R^{11} . In some embodiments, R^{10} is 5-6 membered heterocycloalkyl- C_{1-3} alkylene optionally substituted with 1 or 2 substituents independently selected from R^{11} .

In some embodiments, R^{10} is 5-10 membered heteroaryl- C_{1-3} alkylene optionally substituted with 1 or 2 substituents independently selected from R^{11} . In some embodiments, R^{10} is 6 membered heteroaryl- C_{1-3} alkylene optionally substituted with 1 or 2 substituents independently selected from R^{11} .

In some embodiments, R^{10} is selected from methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, fluoro, methylcarbamoyl, phenyl, piperazinyl, pyrrolidinyl, morpholino, piperidinyl, pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, tetrahydropyranyl, cyclohexyl, 2-morpholinoethyl, pyridinylmethyl, 2,2,2-trifluoroethyl, and imidazo[1,2-a]pyridin-6-yl; wherein said methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methylcarbamoyl, phenyl, piperazinyl, pyrrolidinyl, morpholino, piperidinyl, pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, tetrahydropyranyl, cyclohexyl, 2-morpholinoethyl, pyridinylmethyl, 2,2,2-trifluoroethyl, and imidazo[1,2-a]pyridin-6-yl are each optionally substituted with 1 or 2 substituents independently selected from R^{11} .

In some embodiments, 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, D, CN, OR^{a3} , SR^{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 or 2 substituents independently selected from R^{12} .

In some embodiments, R^{11} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3} , $C(O)NR^{c3}R^{d3}$, $C(O)R^{b3}$, and $NR^{c3}R^{d3}$, wherein said C_{1-6} alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R^{12} .

In some embodiments, R^{11} is independently selected from methyl, ethyl, 2-hydroxyethyl, 1-hydroxypropan-2-yl, tetrahydro-2H-pyran-4-yl, trifluoromethyl, fluoro, 2-

carboxypropan-2-yl, CN, OH, methoxy, dimethylcarbamoyl, methylcarbamoyl, dimethylamine, 1-isobutyryl, morpholino, and pyridinyl.

In some embodiments, R¹¹ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each
5 optionally substituted with 1 or 2 substituents independently selected from R¹².

In some embodiments, R¹¹ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl. In some embodiments, R¹¹ is C₁₋₆ alkyl. In some embodiments, R¹¹ is methyl, ethyl, or propyl. In some embodiments, R¹¹ is methyl.

In some embodiments, R¹² is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, and C(O)OR^{a5}. In some embodiments, R¹² is independently selected from
10 C₁₋₆ alkyl, C(O)OH, and OH.

In some embodiments, R¹⁰ is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, fluoro, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, methylcarbamoyl, 1-methylpyrrolidin-3-yl, 1-(2-hydroxyethyl)pyrrolidin-3-yl, 4-(1-hydroxypropan-2-yl)piperazin-1-yl, 4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl, 4-(2-carboxypropan-2-yl)piperazin-1-yl, 2-methylmorpholino, 3,4-dimethylpiperazin-1-yl, 4-hydroxypiperidin-1-yl, 7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 2-methoxyethyl, tetrahydro-2H-pyran-4-yl, 4-hydroxycyclohexyl, 1-(dimethylcarbamoyl)piperidin-4-yl, 1-isobutyrylpiperidin-4-yl, 2-morpholinoethyl, 4-methylpiperazin-1-yl, pyridin-4-ylmethyl, 2,2,2-trifluoroethyl, pyridin-4-yl, pyridin-3-yl, 4-cyanophenyl, 2-methylpyridin-4-yl, 6-(dimethylamino)pyridin-3-yl, 5-cyanopyridin-3-yl, 6-cyanopyridin-3-yl, imidazo[1,2-a]pyridin-6-yl, 4-cyano-3-methylphenyl, 4-cyano-2-methylphenyl, 4-cyano-3-fluorophenyl, 4-(methylcarbamoyl)phenyl, 4-(dimethylcarbamoyl)phenyl, 3-fluoro-4-(methylcarbamoyl)phenyl, 3-(6-(methylcarbamoyl)pyridin-3-yl, 3-methylpiperazin-1-yl or 4-methylpiperazin-1-yl.
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In some embodiments, R¹⁰ is 3-methylpiperazin-1-yl or 4-methylpiperazin-1-yl. In some embodiments, R¹⁰ is (*R*)-3-methylpiperazin-1-yl.
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In some embodiments, Cy¹ is 6-(3-methylpiperazin-1-yl)pyridin-3-yl, 4-(4-methylpiperazin-1-yl)phenyl, 3-fluoro-4-(4-methylpiperazin-1-yl)phenyl, 6-(4-methylpiperazin-1-yl)pyridin-3-yl, 4-(4-ethylpiperazin-1-yl)-3-methylphenyl, 4-(methylcarbamoyl)phenyl, 4-(1-methylpyrrolidin-3-yl)phenyl, 4-(1-(2-hydroxyethyl)pyrrolidin-3-yl)phenyl, 4-(4-(1-hydroxypropan-2-yl)piperazin-1-yl)phenyl, 4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl, 4-(4-(2-carboxypropan-2-yl)piperazin-1-yl)phenyl, 6-(2-methylmorpholino)pyridin-3-yl, 6-(3,4-dimethylpiperazin-1-yl)pyridin-3-yl, 4-(4-hydroxypiperidin-1-yl)phenyl, 4-(7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-
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yl)phenyl, 1-(2-methoxyethyl)-1H-pyrazol-4-yl, 1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl, 1-(4-hydroxycyclohexyl)-1H-pyrazol-4-yl, 1-(1-(dimethylcarbamoyl)piperidin-4-yl)-1H-pyrazol-4-yl, 1-(1-isobutylpiperidin-4-yl)-1H-pyrazol-4-yl, 1-(2-morpholinoethyl)-1H-pyrazol-4-yl, 6-(4-methylpiperazin-1-yl)pyridin-3-yl, 1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 1-ethyl-1H-pyrazol-4-yl, 1-isopropyl-1H-pyrazol-4-yl, 1-cyclobutyl-1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl, 1-(pyridin-4-yl)-1H-pyrazol-4-yl, 1-(pyridin-3-yl)-1H-pyrazol-4-yl, 1-(4-cyanophenyl)-1H-pyrazol-4-yl, 1-(2-methylpyridin-4-yl)-1H-pyrazol-4-yl, 1-(6-(dimethylamino)pyridin-3-yl)-1H-pyrazol-4-yl, 1-(5-cyanopyridin-3-yl)-1H-pyrazol-4-yl, 1-(6-cyanopyridin-3-yl)-1H-pyrazol-4-yl, 1-(imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-4-yl, 1-(4-cyano-3-methylphenyl)-1H-pyrazol-4-yl, 1-(4-cyano-2-methylphenyl)-1H-pyrazol-4-yl, 1-(4-cyano-3-fluorophenyl)-1H-pyrazol-4-yl, 1-(4-(methylcarbamoyl)phenyl)-1H-pyrazol-4-yl, 1-(4-(dimethylcarbamoyl)phenyl)-1H-pyrazol-4-yl, 1-(3-fluoro-4-(methylcarbamoyl)phenyl)-1H-pyrazol-4-yl, and 1-(6-(methylcarbamoyl)pyridin-3-yl)-1H-pyrazol-4-yl.

In some embodiments, R^2 is selected from H, D, C_{1-4} alkyl, and C_{1-4} haloalkyl.

In some embodiments, R^2 is selected from H and D. In some embodiments, R^2 is H. In some embodiments, R^2 is D.

In some embodiments, Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl 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 if the 4-14 membered heterocycloalkyl contains a fused aromatic ring, then the 4-14 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-14 membered heterocycloalkyl is substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{20} ;

each R^{20} 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, D, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $C(=NR^{e2})R^{b2}$, $C(=NOR^{a2})R^{b2}$, $C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; 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, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

wherein at least one R²⁰ is selected from C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 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}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NOR^{a2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹.

In some embodiments, Cy is 4-14 membered heterocycloalkyl, 4-12 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, 5-12 membered heterocycloalkyl, 5-8 membered heterocycloalkyl, 6-11 membered heterocycloalkyl, 6 membered heterocycloalkyl, 7 membered heterocycloalkyl, 8 membered heterocycloalkyl, 9 membered heterocycloalkyl, 10 membered heterocycloalkyl, or 11 membered heterocycloalkyl wherein the 4-14 membered heterocycloalkyl, 4-12 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, 5-12 membered heterocycloalkyl, 5-8 membered heterocycloalkyl, 6-11 membered heterocycloalkyl, 6 membered heterocycloalkyl, 7 membered heterocycloalkyl, 8 membered heterocycloalkyl, 9 membered heterocycloalkyl, 10 membered heterocycloalkyl, or 11 membered heterocycloalkyl 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 if the 4-14 membered heterocycloalkyl contains a fused aromatic ring, then the 4-14 membered heterocycloalkyl, 4-12 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, 5-12 membered heterocycloalkyl, 5-8 membered heterocycloalkyl, 6-11 membered heterocycloalkyl, 6 membered heterocycloalkyl, 7 membered heterocycloalkyl, 8 membered heterocycloalkyl, 9 membered heterocycloalkyl, 10 membered heterocycloalkyl, or 11 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-14 membered heterocycloalkyl, 4-12 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, 5-12 membered heterocycloalkyl, 5-8 membered heterocycloalkyl, 6-11 membered heterocycloalkyl, 6 membered heterocycloalkyl, 7

membered heterocycloalkyl, 8 membered heterocycloalkyl, 9 membered heterocycloalkyl, 10 membered heterocycloalkyl, or 11 membered heterocycloalkyl is substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, and O; wherein the N are optionally oxidized; wherein if the 4-14 membered heterocycloalkyl contains a fused aromatic ring, then the 4-14 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-14 membered heterocycloalkyl is substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl is a saturated monocyclic ring; wherein the 4-14 membered heterocycloalkyl 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 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-14 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl is a saturated bicyclic ring; wherein the 4-14 membered heterocycloalkyl 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 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-14 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl is a saturated spirocyclic ring; wherein the 4-14 membered heterocycloalkyl 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 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-14 membered

heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, and O; wherein the N are optionally oxidized; wherein if the 4-12 membered heterocycloalkyl contains a fused aromatic ring, then the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl is a saturated monocyclic ring; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl is a saturated bicyclic ring; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 5-12 membered heterocycloalkyl; wherein the 5-12 membered heterocycloalkyl is a saturated spirocyclic ring; wherein the 5-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 5-12 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 6-11 membered heterocycloalkyl; wherein the 6-11 membered heterocycloalkyl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms independently selected from N, and O; wherein the N are optionally oxidized; wherein if the 6-11 membered heterocycloalkyl contains a fused aromatic ring, then
5 the 6-11 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 6-11 membered heterocycloalkyl is substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰.

In some embodiments, Cy is 6-11 membered heterocycloalkyl; wherein the 6-11
10 membered heterocycloalkyl is a saturated monocyclic ring; wherein the 6-11 membered heterocycloalkyl 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 6-11 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 6-11 membered
15 heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 6-11 membered heterocycloalkyl; wherein the 6-11 membered heterocycloalkyl is a saturated bicyclic ring; wherein the 6-11 membered heterocycloalkyl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming
20 heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 6-11 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 6-11 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 6-11 membered heterocycloalkyl; wherein the 6-11 membered heterocycloalkyl is a saturated spirocyclic ring; wherein the 6-11 membered heterocycloalkyl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming
25 heteroatoms independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 6-11 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 6-11 membered
30 heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-8 membered heterocycloalkyl; wherein the 4-8 membered heterocycloalkyl 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 4-8 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-8 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-8 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-8 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-8 membered heterocycloalkyl; wherein the 4-8 membered heterocycloalkyl is a saturated monocyclic ring; wherein the 4-8 membered heterocycloalkyl 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 4-8 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-8 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-8 membered heterocycloalkyl; wherein the 4-8 membered heterocycloalkyl is a saturated bicyclic ring; wherein the 4-8 membered heterocycloalkyl 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 4-8 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 4-8 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 5-8 membered heterocycloalkyl; wherein the 5-8 membered heterocycloalkyl is a saturated spirocyclic ring; wherein the 5-8 membered heterocycloalkyl 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 4-8 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the 5-8 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl 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 the 4-14 membered heterocycloalkyl contains a fused aromatic ring, wherein the 4-14 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-14 membered heterocycloalkyl is substituted with 1, 2, 3, 4
5 or 5 substituents independently selected from R^{20} .

In some embodiments when Cy is a 4-14 membered heterocycloalkyl, 6-11 membered heterocycloalkyl, 4-8 membered heterocycloalkyl, or 5-8 membered heterocycloalkyl, Cy comprises at least one ring-forming N and Cy is attached to the pyrazolopyrimidine core structure through a N of the heterocycloalkyl.

10 In some embodiments, R^{20} is 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, D, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, and $NR^{c2}C(O)OR^{a2}$; 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
15 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} .

In some embodiments, R^{20} is 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, D, OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, and $NR^{c2}R^{d2}$; wherein
20 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 or 2 substituents independently selected from R^{21} .

In some embodiments, R^{20} is selected from C_{1-6} alkyl, C_{6-10} aryl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$; wherein said C_{1-6} alkyl and C_{6-10} aryl are each optionally
25 substituted with 1 or 2 substituents independently selected from R^{21} .

In some embodiments, R^{20} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} .

In some embodiments, R^{20} is C_{1-6} alkyl optionally substituted with 1 or 2 substituents
30 independently selected from R^{21} .

In some embodiments, R^{20} is selected from C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl; wherein said C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} .

In some embodiments, R^{20} is C_{6-10} aryl optionally substituted with 1 or 2 substituents independently selected from R^{21} .

In some embodiments, R^{20} is selected from OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, and $NR^{c2}R^{d2}$. In some embodiments, R^{20} is selected from OR^{a2} , $C(O)R^{b2}$,
 5 $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$.

In some embodiments, R^{20} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, halo, CN, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and C_{6-10} aryl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} .

10 In some embodiments, R^{20} is selected from methyl, ethyl, isopropyl, 2-fluoroethyl, 2,2-difluoroethyl, cyclopropyl, trifluoromethyl, OH, 4-cyanophenyl, pyrrolidine-1-carbonyl, 3-fluoropyrrolidine-1-carbonyl, cyclopropanecarbonyl, isobutyryl, 2-methoxyacetyl, isopropylcarbamoyl, dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, (2-fluoroethoxy)carbonyl.

15 In some embodiments, R^{21} is 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, D, CN, OR^{a4} , SR^{a4} , $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, and $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$; 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
 20 substituted with 1 or 2 substituents independently selected from R^{22} .

In some embodiments, R^{21} is 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, D, CN, and OR^{a4} ; 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
 25 each optionally substituted with 1 or 2 substituents independently selected from R^{22} .

In some embodiments, R^{21} is selected from halo, D, CN, and OR^{a4} . In some embodiments, R^{21} is selected from halo, CN, and OR^{a4} . In some embodiments, R^{21} is selected from F, CN, and OH.

In some embodiments, R^{21} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and
 30 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 or 2 substituents independently selected from R^{22} .

In some embodiments, R^{21} is selected from C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, and 5-10 membered heteroaryl; wherein said C_{3-10} cycloalkyl, 4-

10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R²².

In some embodiments, each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered
5 heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹.

In some embodiments, each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1 or 2 substituents independently selected from R²¹.

In some embodiments, each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl is optionally substituted with 1 or 2
15 substituents independently selected from R²¹.

In some embodiments, each R^{a2}, R^{c2} and R^{d2} is independently selected from C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl; wherein said C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently
20 selected from R²¹.

In some embodiments, any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R²¹.

In some embodiments, each R^{a4}, R^{c4} and R^{d4} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₆ haloalkyl. In some embodiments, each R^{a4}, R^{c4} and R^{d4} is independently selected from H and C₁₋₆ alkyl. In some embodiments, each R^{a4}, R^{c4} and R^{d4} is independently C₁₋₆ alkyl. In some embodiments, each R^{a4}, R^{c4} and R^{d4} is H.
25

In some embodiments, R^{b2} is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents
30 independently selected from R²¹. In some embodiments, R^{b2} is selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl and C₃₋₁₀ cycloalkyl; wherein said C₁₋₆ alkyl and C₃₋₁₀ cycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R²¹. In some embodiments, R^{b2} is selected from C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R²¹. In some embodiments, R^{b2} is C₁₋₆ alkyl optionally substituted with 1 or 2 substituents independently selected from R²¹. In some embodiments, R^{b2} is C₃₋₁₀ cycloalkyl optionally substituted with 1 or 2 substituents independently selected from R²¹. In some embodiments, R^{b2} is 4-10 membered heterocycloalkyl optionally substituted with 1 or 2 substituents independently selected from R²¹.

In some embodiments, Cy is piperidinyl, morpholinyl, azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, piperazinyl, diazabicyclo[3.2.1]octanyl, 1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl, 5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 3-oxopiperazinyl, 5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-7-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-5-yl, 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl, 1,4,5,6,7,8-hexahydro-5,8-epiminocyclohepta[c]pyrazol-9-yl, or 2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl, each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is piperidinyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is morpholinyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is azabicyclo[2.2.1]heptanyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is azabicyclo[3.2.1]octanyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is piperazinyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is diazabicyclo[3.2.1]octanyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 2,5-diazabicyclo[2.2.2]octan-2-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 3-oxopiperazinyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

5 In some embodiments, Cy is 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-7-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

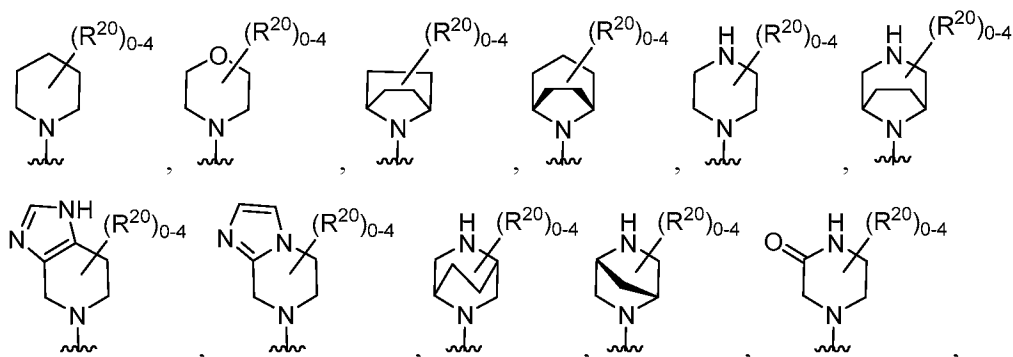
In some embodiments, Cy is 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-5-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

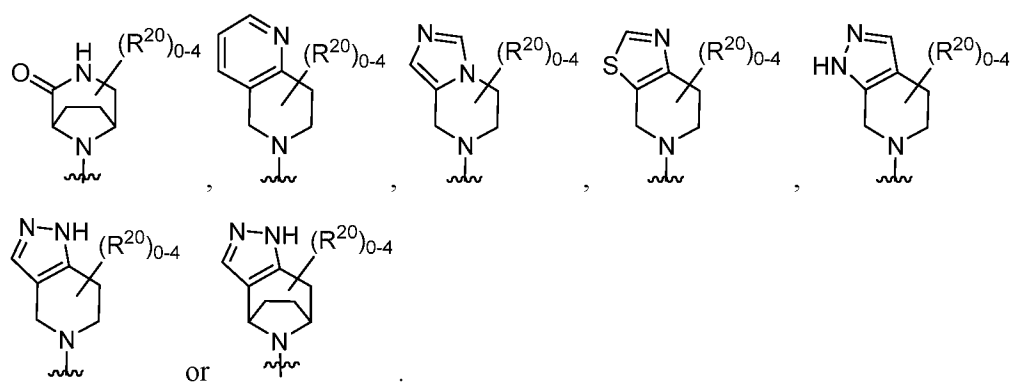
10 In some embodiments, Cy is 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

In some embodiments, Cy is 1,4,5,6,7,8-hexahydro-5,8-epiminocyclohepta[c]pyrazol-9-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰. In some embodiments, Cy is 2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

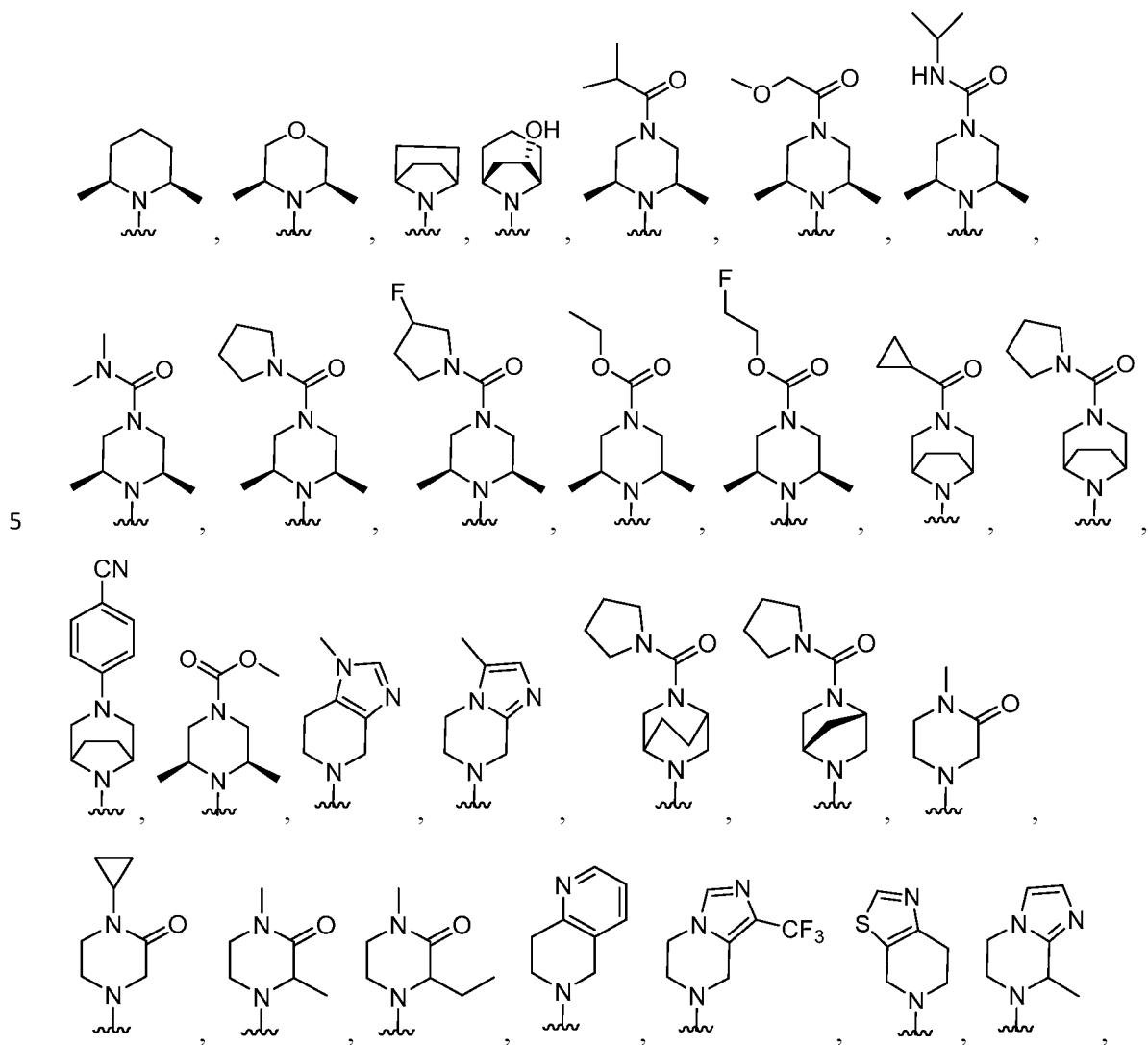
15 In some embodiments, Cy is piperidinyl, morpholinyl, azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, piperazinyl, or diazabicyclo[3.2.1]octanyl. In some embodiments, Cy is piperidinyl. In some embodiments, Cy is morpholinyl. In some embodiments, Cy is azabicyclo[2.2.1]heptanyl. In some embodiments, Cy is azabicyclo[3.2.1]octanyl. In some embodiments, Cy is piperazinyl. In some embodiments, Cy is diazabicyclo[3.2.1]octanyl.

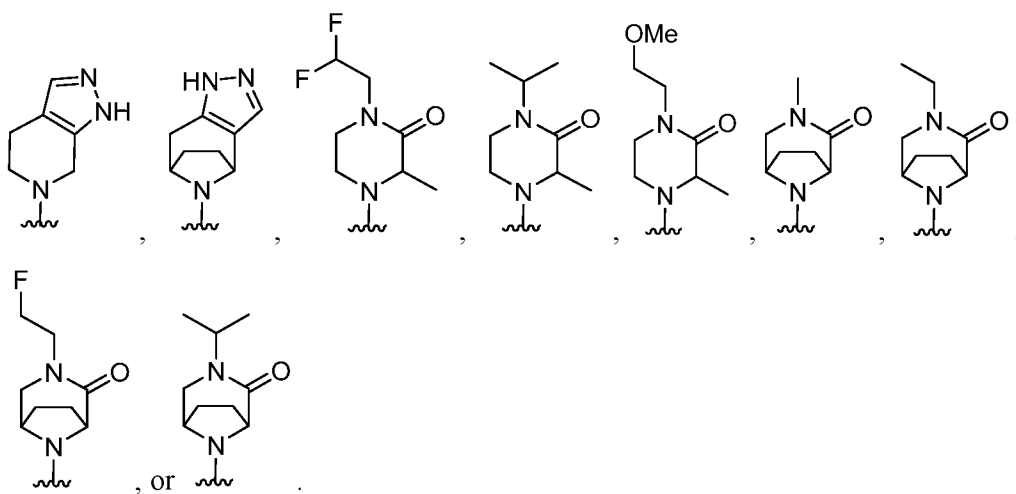
20 In some embodiments, Cy is



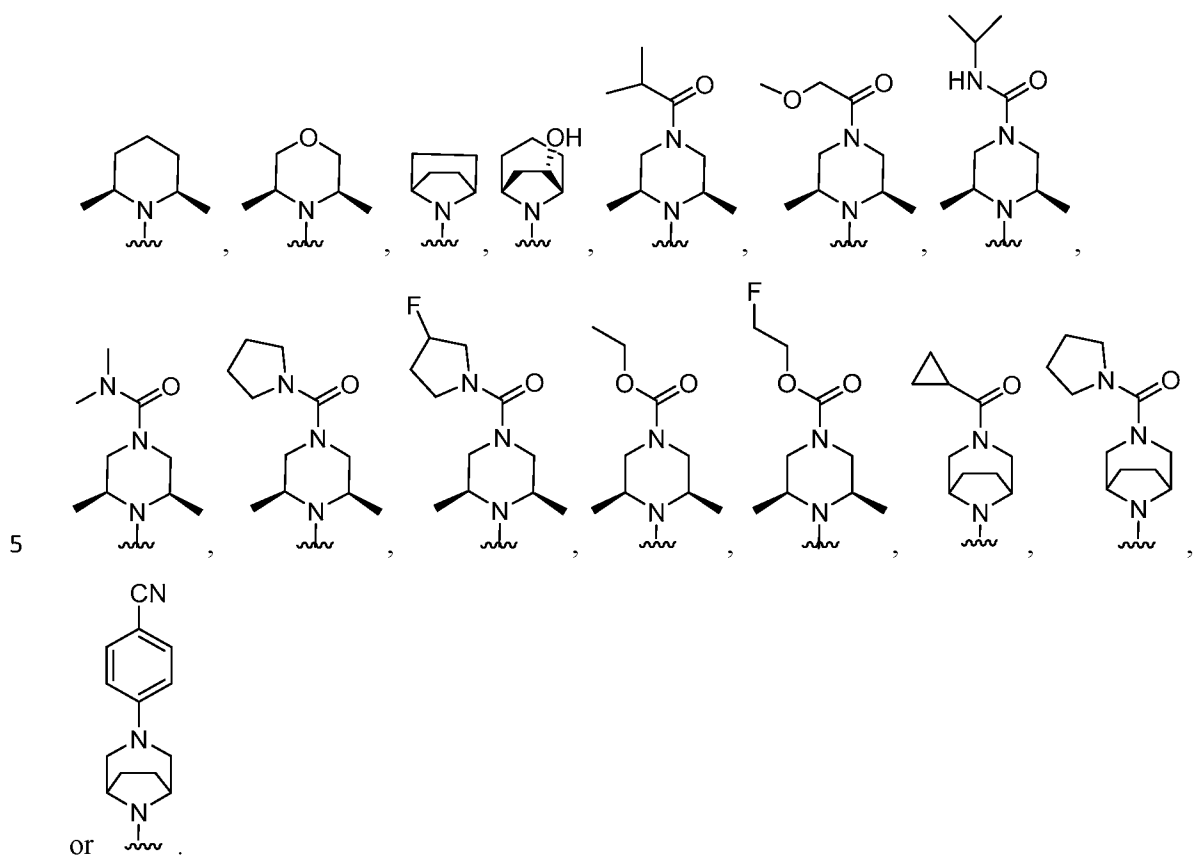


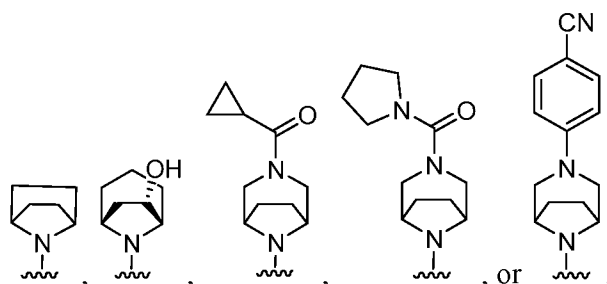
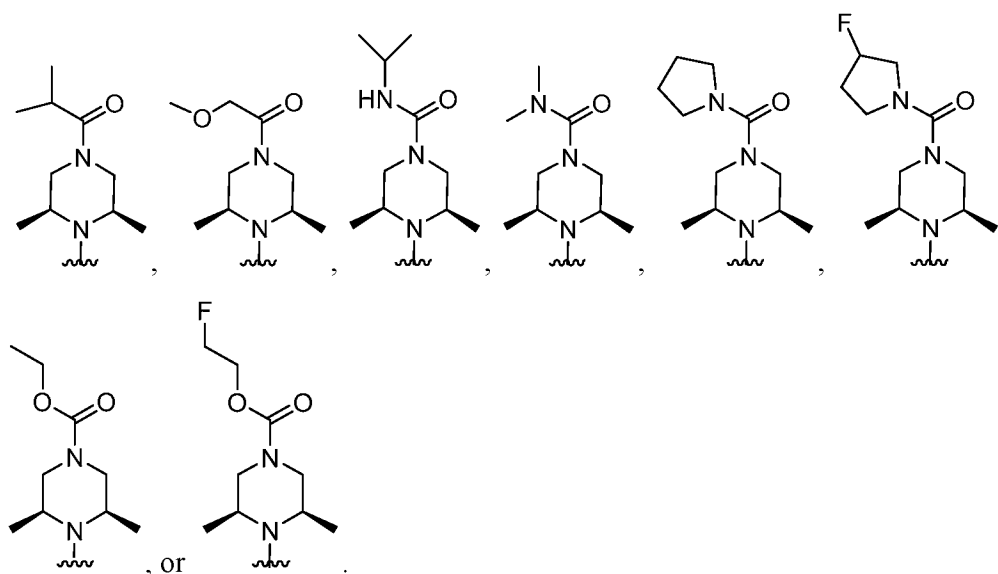
In some embodiments, Cy is





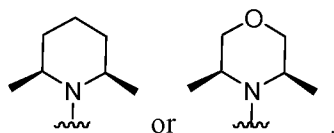
In some embodiments, Cy is



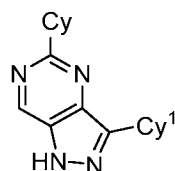


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In some embodiments, Cy is



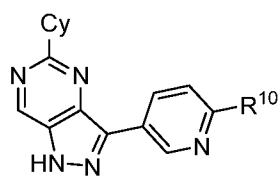
In some embodiments, provided herein is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein Cy and Cy¹ are as defined herein.

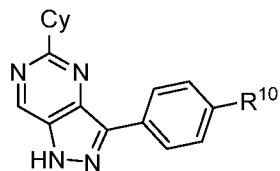
In some embodiments, provided herein is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein Cy and R¹⁰ are as defined herein.

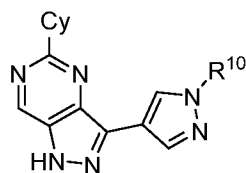
In some embodiments, provided herein is a compound of Formula IV:



IV

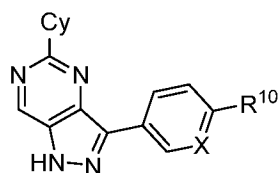
or a pharmaceutically acceptable salt thereof, wherein Cy and R¹⁰ are as defined herein.

In some embodiments, provided herein is a compound of Formula V:



V

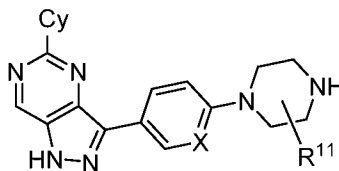
or a pharmaceutically acceptable salt thereof, wherein Cy and R¹⁰ are as defined herein. In some embodiments, provided herein is a compound of Formula VI:



VI

or a pharmaceutically acceptable salt thereof, wherein X is CH, CR¹⁰ or N and Cy and R¹⁰ are as defined herein.

In some embodiments, provided herein is a compound of Formula VII:



VII

or a pharmaceutically acceptable salt thereof, wherein X is CH, CR¹⁰ or N and Cy, R¹⁰ and R¹¹ are as defined herein.

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

5 R¹ is Cy¹;

Cy¹ is selected from C₆₋₁₀ aryl and 5-10 membered heteroaryl; wherein the 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 is
10 optionally substituted by oxo to form a carbonyl group; and wherein the C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R¹⁰;

Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms
15 independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-14 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-14 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the
20 saturated or partially saturated ring; and wherein the 4-14 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰;

R² is H or D;

each R¹⁰ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, 4-10 membered heterocycloalkyl, halo, D, CN, OR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, NR^{c1}R^{d1}, S(O)₂R^{b1}, and
25 S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl and 4-10 membered heterocycloalkyl, are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, D, CN, OR^{a3}, and NR^{c3}R^{d3};

each R²⁰ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, halo, D, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};
30 wherein said C₁₋₆ alkyl and C₆₋₁₀ aryl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

each R²¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, D, CN, OR^{a4} and NR^{c4}R^{d4};

each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{21} ; and

each R^{a4} , R^{c4} and R^{d4} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl.

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

R^1 is Cy^1 ;

Cy^1 is selected from phenyl and 5-6 membered heteroaryl; wherein the 5-6 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 5-6 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the phenyl and 5-6 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R^{10} ;

Cy is 4-8 membered heterocycloalkyl; wherein the 4-8 membered heterocycloalkyl 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 4-8 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-8 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-8 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-8 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from R^{20} ;

R^2 is H or D;

each R^{10} is 4-10 membered heterocycloalkyl optionally substituted with 1 or 2 substituents independently selected from R^{11} ;

each R^{11} is C_{1-6} alkyl;

each R^{20} is independently selected from C_{1-6} alkyl, C_{6-10} aryl, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$; wherein said C_{1-6} alkyl and C_{6-10} aryl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{21} is independently selected from halo, D, CN, and OR^{a4} ;

5 each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

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 4-10 membered heterocycloalkyl group optionally substituted with
10 1 or 2 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ; and

15 R^{a4} is C_{1-6} alkyl.

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

R^1 is Cy^1 ;

Cy^1 is selected from C_{5-6} cycloalkyl, 5-6 membered heterocycloalkyl, phenyl and 5-6
20 membered heteroaryl; wherein the 5-6 membered heterocycloalkyl and 5-6 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 5-6 membered heteroaryl and 5-6 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and
25 wherein the C_{5-6} cycloalkyl, 5-6 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{10} ;

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl has at least one ring-forming carbon atom and 1, 2, 3, or 4 ring-forming heteroatoms
30 independently selected from N, O, and S; wherein the N and S are optionally oxidized; wherein a ring-forming carbon atom of 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the

saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰;

R² is selected from H, D, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

each R¹⁰ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, and NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3}, C(O)NR^{c3}R^{d3}, C(O)R^{b3}, and NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹²;

each R¹² is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, and C(O)OR^{a5};

each R²⁰ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, CN, NO₂, 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}, and NR^{c2}C(O)OR^{a2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R²¹ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, CN, and OR^{a4};

each R^{a1}, R^{c1} and R^{d1} is independently selected from H, and C₁₋₆ alkyl;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R¹¹;

each R^{b1} is independently selected from C₁₋₆ alkyl;

each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

5 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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently
10 selected from R^{21} ;

each R^{a3} , R^{c3} and R^{d3} is independently selected from H, C_{1-6} alkyl, 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_{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
15 selected from R^{12} ;

or any R^{c3} and R^{d3} 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^{12} ;

each R^{b3} is independently selected from C_{1-6} alkyl, 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_{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} is independently selected from H, and C_{1-6} alkyl; and

each R^{a5} is independently selected from H, and C_{1-6} alkyl.

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

R^1 is Cy^1 ;

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

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R²⁰;

R² is H or D;

each R¹⁰ is independently selected from C₁₋₆ alkyl, halo, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, and C(O)NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3}, C(O)NR^{c3}R^{d3}, C(O)R^{b3}, and NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹²;

each R^{c1} and R^{d1} is independently selected from H, and C₁₋₆ alkyl;

each R^{a3}, R^{b3}, R^{c3} and R^{d3} is independently selected from H, and C₁₋₆ alkyl;

each R¹² is independently selected from C₁₋₆ alkyl, C(O)OH, and OH;

each R²⁰ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, halo, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, and C(O)OR^{a2}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and C₆₋₁₀ aryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl is optionally substituted with 1 or 2 substituents independently selected from R²¹;

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 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{21} is independently selected from halo, D, CN, and OR^{a4} ; and

each R^{a4} is C_{1-6} alkyl.

10 In some embodiments, provided herein is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

Cy^1 is pyrazolyl, phenyl or pyridinyl, wherein the pyrazolyl, phenyl or pyridinyl are each optionally substituted with 1 or 2 substituents independently selected from R^{10} ;

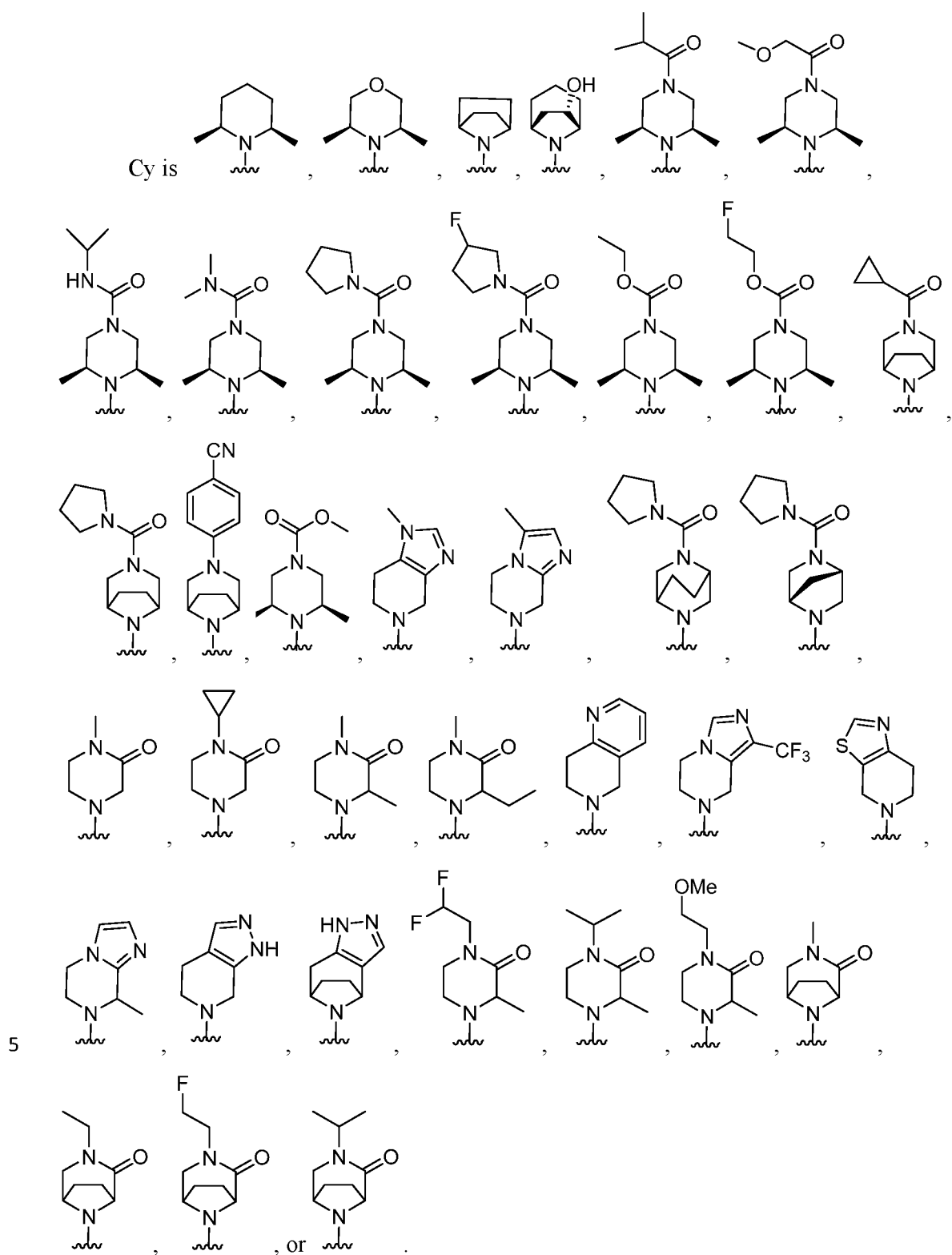
Cy is piperidinyl, morpholinyl, azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, 15 piperazinyl, diazabicyclo[3.2.1]octanyl, 1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl, 5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 3-oxopiperazinyl, 5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-7-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-5-yl, 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl, 1,4,5,6,7,8-hexahydro-5,8-epiminocyclohepta[c]pyrazol-9-yl, or 2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl, each 20 optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{20} ;

each R^{10} is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, fluoro, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, methylcarbamoyl, 1-methylpyrrolidin-3-yl, 1-(2-hydroxyethyl)pyrrolidin-3-yl, 4-(1-hydroxypropan-2-yl)piperazin-1-yl, 4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl, 4-(2-carboxypropan-2-yl)piperazin-1-yl, 2-methylmorpholino, 3,4-dimethylpiperazin-1-yl, 4-hydroxypiperidin-1-yl, 7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 2-methoxyethyl, tetrahydro-2H-pyran-4-yl, 4-hydroxycyclohexyl, 1-(dimethylcarbamoyl)piperidin-4-yl, 1-isobutyrylpiperidin-4-yl, 2-morpholinoethyl, 4-methylpiperazin-1-yl, pyridin-4-ylmethyl, 2,2,2-trifluoroethyl, pyridin-4-yl, pyridin-3-yl, 4-cyanophenyl, 2-methylpyridin-4-yl, 6-(dimethylamino)pyridin-3-yl, 5-cyanopyridin-3-yl, 6-cyanopyridin-3-yl, imidazo[1,2-a]pyridin-6-yl, 4-cyano-3-methylphenyl, 4-cyano-2-methylphenyl, 4-cyano-3-fluorophenyl, 4-(methylcarbamoyl)phenyl, 4-(dimethylcarbamoyl)phenyl, 3-fluoro-4-(methylcarbamoyl)phenyl, 3-(6-(methylcarbamoyl)pyridin-3-yl, 3-methylpiperazin-1-yl or 4-methylpiperazin-1-yl; and

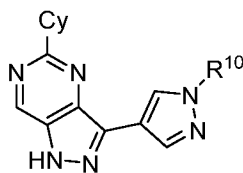
each R²⁰ is independently selected from methyl, ethyl, isopropyl, 2-fluoroethyl, 2,2-difluoroethyl, cyclopropyl, trifluoromethyl, OH, 4-cyanophenyl, pyrrolidine-1-carbonyl, 3-fluoropyrrolidine-1-carbonyl, cyclopropanecarbonyl, isobutyryl, 2-methoxyacetyl, isopropylcarbamoyl, dimethylcarbamoyl, methoxycarbonyl, ethoxycarbonyl, (2-fluoroethoxy)carbonyl.

In some embodiments, provided herein is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

Cy¹ is 6-(3-methylpiperazin-1-yl)pyridin-3-yl, 4-(4-methylpiperazin-1-yl)phenyl, 3-fluoro-4-(4-methylpiperazin-1-yl)phenyl, 6-(4-methylpiperazin-1-yl)pyridin-3-yl, 4-(4-ethylpiperazin-1-yl)-3-methylphenyl, 4-(methylcarbamoyl)phenyl, 4-(1-methylpyrrolidin-3-yl)phenyl, 4-(1-(2-hydroxyethyl)pyrrolidin-3-yl)phenyl, 4-(4-(1-hydroxypropan-2-yl)piperazin-1-yl)phenyl, 4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl, 4-(4-(2-carboxypropan-2-yl)piperazin-1-yl)phenyl, 6-(2-methylmorpholino)pyridin-3-yl, 6-(3,4-dimethylpiperazin-1-yl)pyridin-3-yl, 4-(4-hydroxypiperidin-1-yl)phenyl, 4-(7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl, 1-(2-methoxyethyl)-1H-pyrazol-4-yl, 1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl, 1-(4-hydroxycyclohexyl)-1H-pyrazol-4-yl, 1-(1-(dimethylcarbamoyl)piperidin-4-yl)-1H-pyrazol-4-yl, 1-(1-isobutyrylpiperidin-4-yl)-1H-pyrazol-4-yl, 1-(2-morpholinoethyl)-1H-pyrazol-4-yl, 6-(4-methylpiperazin-1-yl)pyridin-3-yl, 1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 1-ethyl-1H-pyrazol-4-yl, 1-isopropyl-1H-pyrazol-4-yl, 1-cyclobutyl-1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl, 1-(pyridin-4-yl)-1H-pyrazol-4-yl, 1-(pyridin-3-yl)-1H-pyrazol-4-yl, 1-(4-cyanophenyl)-1H-pyrazol-4-yl, 1-(2-methylpyridin-4-yl)-1H-pyrazol-4-yl, 1-(6-(dimethylamino)pyridin-3-yl)-1H-pyrazol-4-yl, 1-(5-cyanopyridin-3-yl)-1H-pyrazol-4-yl, 1-(6-cyanopyridin-3-yl)-1H-pyrazol-4-yl, 1-(imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-4-yl, 1-(4-cyano-3-methylphenyl)-1H-pyrazol-4-yl, 1-(4-cyano-2-methylphenyl)-1H-pyrazol-4-yl, 1-(4-cyano-3-fluorophenyl)-1H-pyrazol-4-yl, 1-(4-(methylcarbamoyl)phenyl)-1H-pyrazol-4-yl, 1-(4-(dimethylcarbamoyl)phenyl)-1H-pyrazol-4-yl, 1-(3-fluoro-4-(methylcarbamoyl)phenyl)-1H-pyrazol-4-yl, 1-(6-(methylcarbamoyl)pyridin-3-yl)-1H-pyrazol-4-yl; and



In some embodiments, provided herein is a compound of Formula V



V,

or a pharmaceutically acceptable salt thereof, wherein:

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl

5 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is
10 directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R²⁰;

R¹⁰ is selected from C₁₋₆ alkyl, halo, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃
15 alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, and C(O)NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, 4-10
20 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3}, C(O)NR^{c3}R^{d3}, C(O)R^{b3}, and NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹²;

each R^{c1} and R^{d1} is independently selected from H, and C₁₋₆ alkyl;

25 each R^{a3}, R^{b3}, R^{c3} and R^{d3} is independently selected from H, and C₁₋₆ alkyl;

each R¹² is independently selected from C₁₋₆ alkyl, C(O)OH, and OH;

each R²⁰ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, halo, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, and C(O)OR^{a2}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and C₆₋₁₀ aryl are each optionally substituted with 1 or 2 substituents
30 independently selected from R²¹;

each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

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 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{21} is independently selected from halo, D, CN, and OR^{a4} ; and

each R^{a4} is C_{1-6} alkyl.

In some embodiments, provided herein is a compound of Formula V, or a pharmaceutically acceptable salt thereof, wherein:

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R^{20} ;

R^{10} is methyl;

each R^{20} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, halo, CN, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and C_{6-10} aryl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

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 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

- 5 each R^{21} is independently selected from halo, D, CN, and OR^{a4} ; and
 each R^{a4} is C_{1-6} alkyl.

In some embodiments, provided herein is a compound of Formula VI, or a pharmaceutically acceptable salt thereof wherein:

X is selected from CH, CF, CCH_3 and N;

- 10 Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered
- 15 heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R^{20} ;

- R^{10} is selected from 4-10 membered heterocycloalkyl, wherein said 4-10 membered
- 20 heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from R^{11} ;

 each R^{11} is independently selected from C_{1-6} alkyl, and 4-10 membered heterocycloalkyl, C_{1-6} alkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{12} ;

- 25 each R^{12} is independently selected from C_{1-6} alkyl, $C(O)OH$, and OH;

 each R^{20} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, halo, CN, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and C_{6-10} aryl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

- 30 each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

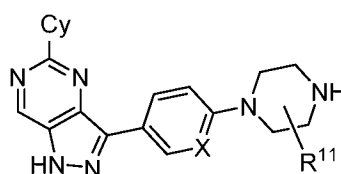
or any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{21} is independently selected from halo, D, CN, and OR^{a4} ; and

each R^{a4} is C_{1-6} alkyl.

In some embodiments, provided herein is a compound of Formula VII, or a pharmaceutically acceptable salt thereof



VII

wherein:

X is selected from CH, CF, CCH_3 and N;

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R^{20} ;

R^{11} is selected from C_{1-6} alkyl, and 4-10 membered heterocycloalkyl, C_{1-6} alkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{12} ;

each R^{12} is independently selected from C_{1-6} alkyl, $C(O)OH$, and OH;

each R^{20} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, halo, CN, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$; wherein said C_{1-6} alkyl, C_{3-10}

cycloalkyl, and C₆₋₁₀ aryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl is optionally substituted with 1 or 2 substituents independently

5 selected from R²¹;

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 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{b2} is independently selected from C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R²¹ is independently selected from halo, D, CN, and OR^{a4}; and

each R^{a4} is C₁₋₆ alkyl.

15 In some embodiments, provided herein is a compound selected from:

5-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)-3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine;

(3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)morpholine;

20 5-(7-azabicyclo[2.2.1]heptan-7-yl)-3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine;

(1*R*,5*S*,6*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-6-ol;

1-((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)-2-methylpropan-1-one;

1-((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)-2-methoxyethan-1-one;

(3*R*,5*S*)-*N*-isopropyl-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxamide;

30 (3*R*,5*S*)-*N,N*,3,5-tetramethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxamide;

((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone;

((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)(3-fluoropyrrolidin-1-yl)methanone;

Ethyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate;

5 2-Fluoroethyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate;

Cyclopropyl((1*R*,5*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)methanone;

10 ((1*R*,5*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)(pyrrolidin-1-yl)methanone;

4-((1*R*,5*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)benzonitrile; and

5-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine,

15 or a pharmaceutically acceptable salt thereof.

In some embodiments, provided herein is a compound selected from:

Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate;

20 (*R*)-5-(1-Methyl-1,4,6,7-tetrahydro-5*H*-imidazo[4,5-*c*]pyridin-5-yl)-3-(6-(3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine;

(*R*)-5-(3-Methyl-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-3-(6-(3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine;

(5-(3-(6-((*R*)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)(pyrrolidin-1-yl)methanone;

25 ((1*S*,4*S*)-5-(3-(6-((*R*)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)(pyrrolidin-1-yl)methanone

Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate;

30 Methyl (3*R*,5*S*)-4-(3-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate;

Methyl (3*R*,5*S*)-4-(3-(4-(4-ethylpiperazin-1-yl)-3-methylphenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(methylcarbamoyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(1-methylpyrrolidin-3-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

5 Methyl (3R,5S)-4-(3-(4-(1-(2-hydroxyethyl)pyrrolidin-3-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(4-(4-(1-hydroxypropan-2-yl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

10 Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

2-(4-(4-(5-((2R,6S)-4-(Methoxycarbonyl)-2,6-dimethylpiperazin-1-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperazin-1-yl)-2-methylpropanoic acid;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(6-((R)-2-methylmorpholino)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

15 Methyl (3R,5S)-4-(3-(6-((R)-3,4-dimethylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

20 Methyl (3R,5S)-4-(3-(4-((7S,8aR)-7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

1-Methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

1-Cyclopropyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

25 1,3-Dimethyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

3-Ethyl-1-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

30 6-(3-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

3-(1-Methyl-1H-pyrazol-4-yl)-5-(1-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1H-pyrazolo[4,3-d]pyrimidine;

5-(3-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine;

3-(1-Methyl-1H-pyrazol-4-yl)-5-(8-methyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-1H-pyrazolo[4,3-d]pyrimidine;

3-(1-Methyl-1H-pyrazol-4-yl)-5-(1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl)-1H-pyrazolo[4,3-d]pyrimidine;

5 9-(3-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[c]pyrazole;

1-(2,2-Difluoroethyl)-3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

1-Isopropyl-3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

10 1-(2-Methoxyethyl)-3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

3-Methyl-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

15 3-Ethyl-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-(2-Fluoroethyl)-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Isopropyl-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

25 8-(3-(1-((1R,4S)-4-Hydroxycyclohexyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

N,N-Dimethyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxamide;

8-(3-(1-(1-Isobutyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-Ethyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

5 8-(3-(1-Isopropyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-Cyclobutyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-Cyclopropyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

10 3-Methyl-8-(3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

15 3-Methyl-8-(3-(1-(pyridin-3-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

4-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

3-Methyl-8-(3-(1-(2-methylpyridin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

20 8-(3-(1-(6-(Dimethylamino)pyridin-3-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

5-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)nicotinonitrile;

25 5-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)picolinonitrile;

8-(3-(1-(Imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

2-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

30 3-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

2-Fluoro-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

N,N-Dimethyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide;

N-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide;

5 2-Fluoro-N-methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide; and

N-Methyl-5-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)picolinamide;

or a pharmaceutically acceptable salt thereof.

10 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
15 in any suitable subcombination. Thus, it is contemplated as features described as embodiments of the compounds of Formula (I) can be combined in any suitable combination.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include each and every individual subcombination of the members of such groups and ranges. For
20 example, the term "C₁₋₆ alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl and C₆ alkyl.

The term "n-membered," where n is an integer, typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidiny1 is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of
25 a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

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

is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless
5 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"
10 means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms.

The term " C_{n-m} " indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-4} , C_{1-6} and the like.

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

The term "alkenyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or
25 more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term " C_{n-m} alkenyl" refers to an alkenyl group having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl and the like.
30

The term "alkynyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with

one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. The term " C_{n-m} alkynyl" refers to an alkynyl group having n to m carbons.

Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3

5 carbon atoms.

The term "alkylene", employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkylene group to the remainder of the compound. The term " C_{n-m} alkylene" refers to an alkylene group having n to m carbon atoms.

10 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.

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

15

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

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

20

As used herein, the term "carbamyl" refers to a group of formula $-C(O)NH_2$.

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

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

25

As used herein, the term "cyano- C_{1-3} alkyl" refers to a group of formula $-(C_{1-3} \text{ alkylene})-CN$.

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

30

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

atoms. Example haloalkyl groups include CF₃, C₂F₅, CHF₂, CH₂F, CCl₃, CHCl₂, C₂Cl₅ and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

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

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

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

As used herein, the term "C_{n-m} alkylamino" refers to a group of formula -NH(alkyl),
15 wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkoxy carbonyl" refers to a group of formula -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

20 As used herein, the term "C_{n-m} alkyl carbonyl" refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkyl carbonylamino" refers to a group of formula -NHC(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some
25 embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkyl sulfonylamino" refers to a group of formula -NHS(O)₂-alkyl, wherein the alkyl group has n to m carbon atoms. In some
embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "aminosulfonyl" refers to a group of formula -S(O)₂NH₂.

30 As used herein, the term "C_{n-m} alkyl aminosulfonyl" refers to a group of formula -S(O)₂NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "di(C_{n-m} alkyl) aminosulfonyl" refers to a group of formula -S(O)₂N(alkyl)₂, wherein each alkyl group independently has n to m carbon atoms.

In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminosulfonylamino” refers to a group of formula -NHS(O)₂NH₂.

5 As used herein, the term “C_{n-m} alkylaminosulfonylamino” refers to a group of formula -NHS(O)₂NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} alkyl)aminosulfonylamino” refers to a group of formula -NHS(O)₂N(alkyl)₂, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “aminocarbonylamino”, employed alone or in combination with other terms, refers to a group of formula -NHC(O)NH₂.

As used herein, the term “C_{n-m} alkylaminocarbonylamino” refers to a group of formula -NHC(O)NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m} alkyl)aminocarbonylamino” refers to a group of formula -NHC(O)N(alkyl)₂, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkylcarbonyl” refers to a group of formula -C(O)-NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “di(C_{n-m}-alkyl)carbonyl” refers to a group of formula -C(O)N(alkyl)₂, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

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

As used herein, the term “C_{n-m} alkylthio” refers to a group of formula -S-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkylsulfinyl” refers to a group of formula -S(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfonyl" refers to a group of formula -S(O)₂-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

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

The term "aryl," employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (*e.g.*, having 2 fused rings). The term "C_{n-m} aryl" refers to an aryl group having from n to m ring carbon atoms.
10 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.

The term "heteroaryl" or "heteroaromatic," employed alone or in combination with
15 other terms, refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen, nitrogen and phosphorous. 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
20 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 5-12 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 5-11 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently
25 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
30 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, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1,2-*b*]thiazolyl, purinyl, pyrazolopyrimidinyl (including pyrazolo[1,5-*a*]pyrimidine and pyrazolo[4,3-*d*]pyrimidinyl), imidazopyrindinyl (i.e. imidazo[1,2-*a*]pyridinyl) and the like. In some embodiments, the heteroaryl group is pyridone (e.g., 2-pyridone). Exemplary
5 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. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl, isoindolyl, and pyridazinyl.

10 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
15 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
20 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
25 can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or
30 cyclohexyl.

The term "heterocycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain one or more alkenylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from nitrogen, sulfur, oxygen and phosphorus, and which has

4-14 ring members, 4-12 ring members, 4-10 ring members, 4-8 ring members, 4-7 ring members, 4-6 ring members, 6-11 ring members, 5-12 ring members, 5-8 ring members or any ranges therebetween. 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)₂, *N*-oxide *etc.*) or a nitrogen atom can be quaternized. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the heterocycloalkyl ring, *e.g.*, benzo or thienyl derivatives of piperidine, morpholine, azepine, *etc.* A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of heterocycloalkyl groups include azetidiny, azepanyl, dihydrobenzofuranyl, dihydrofuranyl, dihydropyranyl, morpholino, 3-oxa-9-azaspiro[5.5]undecanyl, 1-oxa-8-azaspiro[4.5]decanyl, piperidiny, piperaziny, oxopiperaziny, pyranyl, pyrrolidiny, quinuclidiny, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,4-tetrahydroquinoliny, 1,2,3,4-tetrahydroisoquinoliny, 1,2,3,4-tetrahydronaphthyl, 2,3-dihydro-1H-inden-5-yl, isoindoliny, tropanyl, and thiomorpholino. Additional Examples of heterocycloalkyl groups include azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, diazabicyclo[3.2.1]octanyl, 1,4,6,7-tetrahydro-5H-imidazo[4,5-*c*]pyridin-5-yl, 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8H)-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 3-oxopiperaziny, 5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl, 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-7-yl, 4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-5-yl, 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*c*]pyridin-6-yl, 1,4,5,6,7,8-hexahydro-5,8-epiminocyclohepta[*c*]pyrazol-9-yl, and 2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl.

At certain places, the definitions or embodiments refer to specific rings (*e.g.*, an azetidine ring, a pyridine ring, *etc.*). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an

azetidine ring may be attached at any position of the ring, whereas an azetidin-3-yl ring is attached at the 3-position.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless
5 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
10 compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. One method includes fractional recrystallization using a chiral
15 resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, *e.g.*, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as δ -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods
20 include stereoisomerically pure forms of α -methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, *N*-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane and the like.

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

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

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example

prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, *e.g.*, 1*H*- and 3*H*-imidazole, 1*H*-, 2*H*- and 4*H*- 1,2,4-triazole, 1*H*- and 2*H*- isoindole and 1*H*- and 2*H*-pyrazole. Tautomeric forms can be in
5 equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention can be replaced
10 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
15 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,
20 metabolism experiments, and/or assays.

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.*
25 **2015**, 58, 308-312).

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
30 combination thereof.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or can be isolated. When in the solid state, the compounds described herein and salts thereof may occur in various forms and may, *e.g.*, take the form of solvates, including hydrates. The compounds

may be in any solid state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid state form of the compound.

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

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

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

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, *e.g.*, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (*e.g.*, methanol, ethanol, iso-propanol or butanol) or acetonitrile (MeCN) are

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

Synthesis

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

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

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

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.*, ¹H or ¹³C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

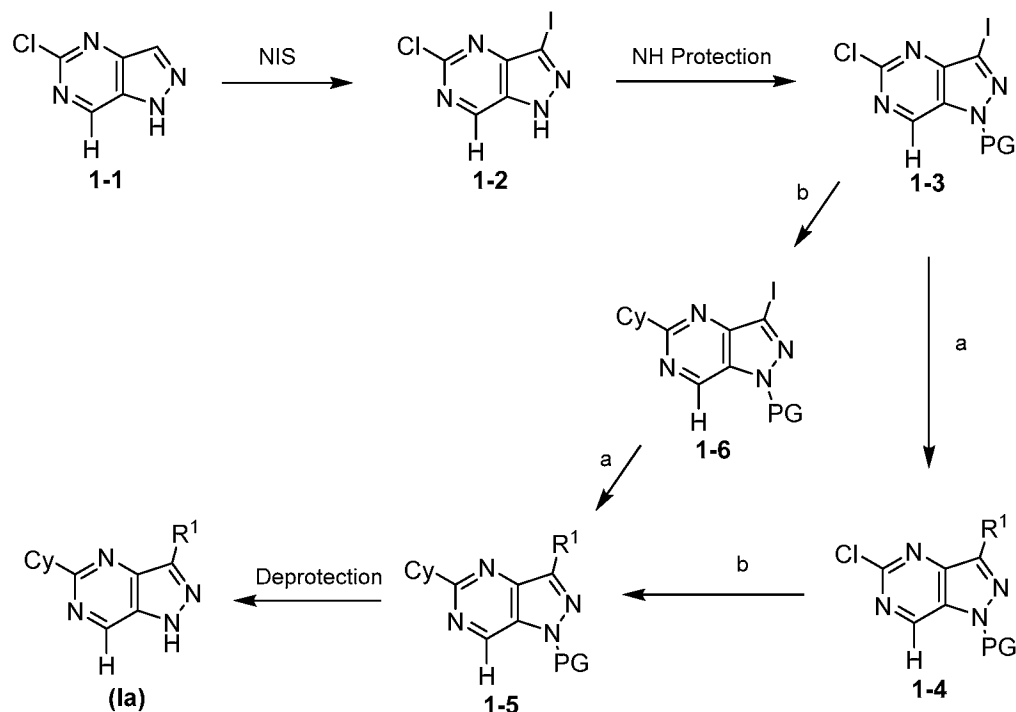
The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations

shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

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

5 Compounds of Formula (Ia) (compounds of Formula (I) wherein R² is H) with a variety of substitution at positions R¹ and Cy such as those described herein can be prepared, using a process as illustrated in **Scheme 1**. Iodination of 5-chloro-1*H*-pyrazolo[4,3-*d*]pyrimidine (**1-1**) with one of the iodination agents, such as iodine or NIS, forms compounds of Formula (**1-2**). The NH group of the pyrazole ring of the compounds of
10 Formula (**1-2**) is protected with a suitable protecting group (*e.g.*, Boc or SEM) to form compounds of Formula (**1-3**). The iodo substituent in the compounds of Formula (**1-3**) can be converted into R¹ via a number of different cross-coupling reactions, including Suzuki, Sonogashira, Negishi, Buchwald–Hartwig amination, Cu-catalyzed amination and others, to give the compounds of Formula (**1-4**). The chloro substituent in the compounds of Formula
15 (**1-4**) can be further converted into Cy via a nucleophilic aromatic substitution (*e.g.*, S_NAr) or a number of different cross-coupling reactions, including Buchwald–Hartwig amination, Suzuki, Stille, Negishi, Cu-catalyzed amination and others, to give the compounds of Formula (**1-5**). Finally, deprotection of the protecting group, *e.g.* under acidic conditions, such as treatment with HCl or TFA, and/or under basic conditions such as treatment with
20 aqueous ammonium hydroxide results in the formation of the desired compounds of Formula (Ia). Alternatively, compounds of Formula (**1-5**) can be prepared from compounds of Formula (**1-3**) by first conducting a nucleophilic aromatic substitution (*e.g.*, S_NAr) or a cross-coupling reaction, including Buchwald–Hartwig amination, Suzuki, Cu-catalyzed amination and others to generate compounds of Formula (**1-6**), followed by a number of different cross-coupling reactions, including Suzuki, Sonogashira, Negishi, Buchwald–Hartwig amination,
25 Cu-catalyzed amination and others, to convert the iodo substituent into R¹.

Scheme 1



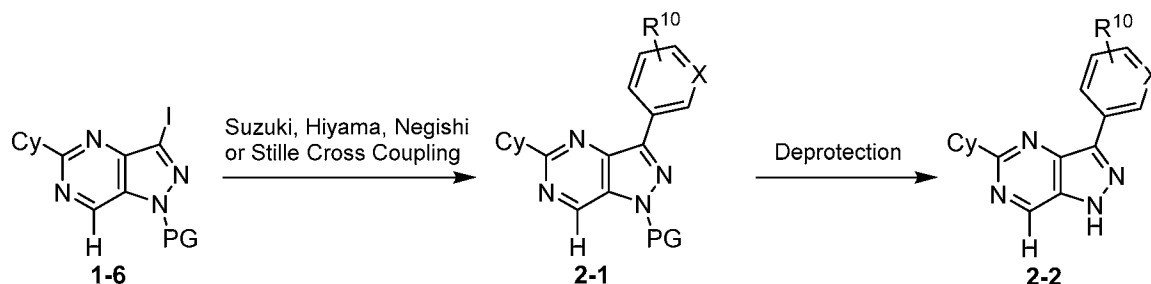
(a) Suzuki, Stille, Negishi or Cu cat. amination

(b) S_NAr reaction, Buchwald-Hartwig, Suzuki, Stille, Negishi or Cu cat. amination

Compounds of Formula (2-2) (compounds of Formula (I) wherein R² is H and Cy¹ is phenyl or pyridinyl with X is CH or N) with a variety of substitution at positions Cy and R¹⁰ such as those described herein can be prepared, using a process as illustrated in **Scheme 2**.

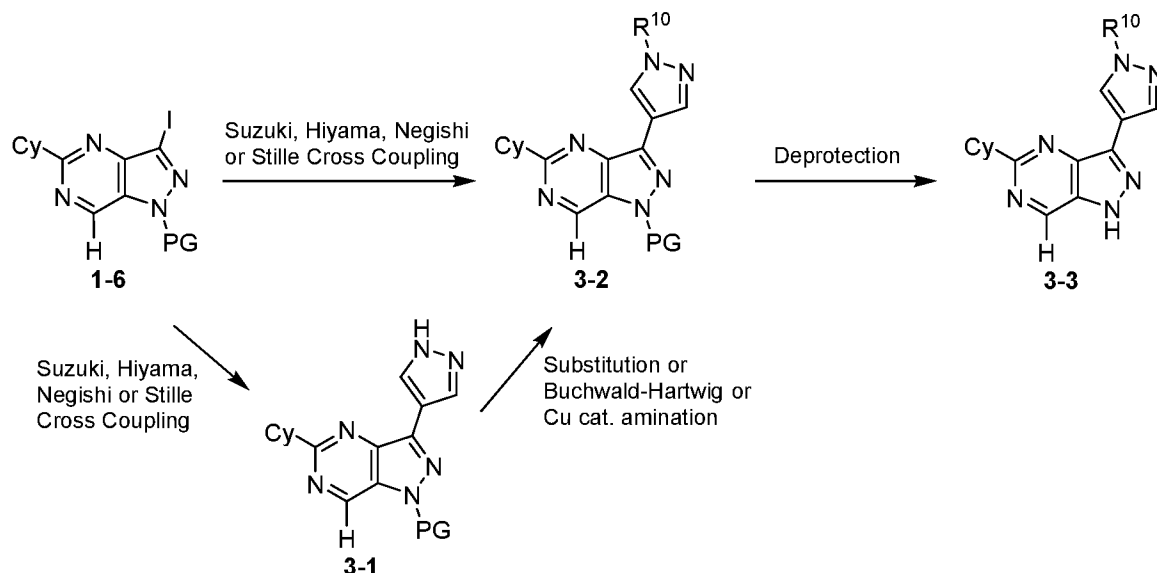
Compounds of Formula (1-6) can be converted to compounds of Formula (2-1) via a number of different cross-coupling reactions with a suitable coupling reagent in the presence of a suitable palladium catalyst and a suitable base, including Suzuki, Hiyama, Negishi, Stille cross-coupling reactions and others. Deprotection of the protecting group, *e.g.* under acidic conditions, such as treatment with HCl or TFA, and/or under basic conditions such as treatment with aqueous ammonium hydroxide results in the formation of the desired compounds of Formula (2-2).

Scheme 2



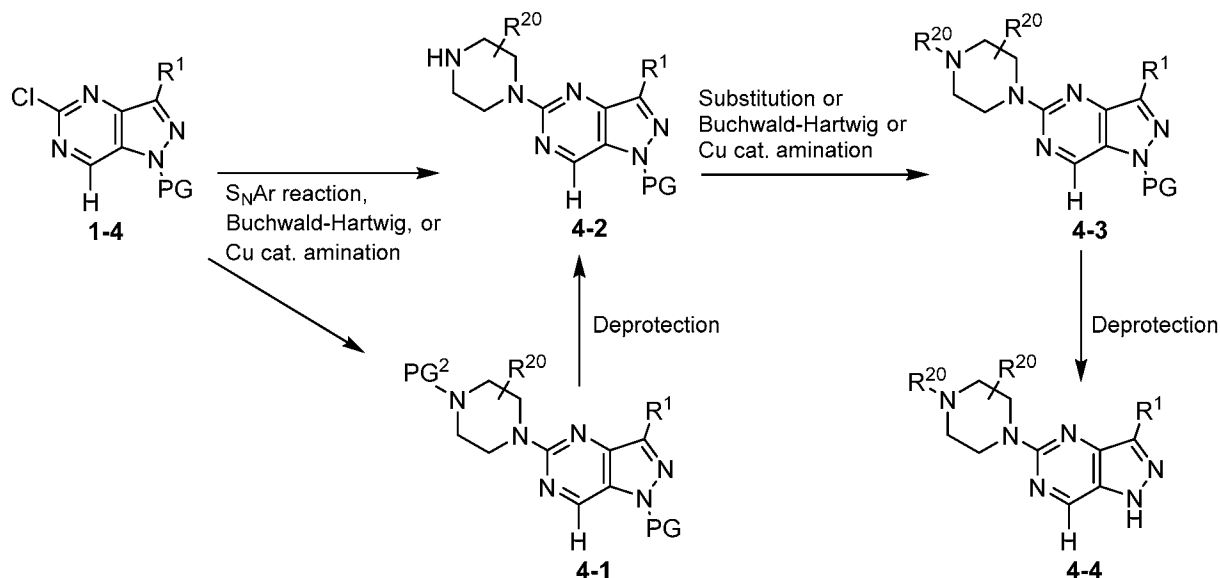
Compounds of Formula (3-3) (compounds of Formula (I) wherein R² is H and Cy¹ is pyrazol) with a variety of substitution at positions Cy and R¹⁰ such as those described herein can be prepared, using a process as illustrated in **Scheme 3**. Compounds of Formula (1-6) can be converted to compounds of Formula (3-1) via a number of different cross-coupling reactions with a suitable coupling reagent in the presence of a suitable palladium catalyst and a suitable base, including Suzuki, Hiyama, Negishi, Stille cross-coupling reactions and others. Compounds of Formula (3-1) can be converted to compounds of Formula (3-2) via a substitution reaction or a cross-coupling reaction, including Buchwald–Hartwig amination, Cu-catalyzed amination and others. Alternatively, compounds of Formula (3-2) can be prepared directly from compounds of Formula (1-6) by a number of different cross-coupling reactions with a suitable coupling reagent in the presence of a suitable palladium catalyst and a suitable base, including Suzuki, Hiyama, Negishi, Stille cross-coupling reactions and others. Deprotection of the protecting group, *e.g.* under acidic conditions, such as treatment with HCl or TFA, and/or under basic conditions such as treatment with aqueous ammonium hydroxide results in the formation of the desired compounds of Formula (3-3).

Scheme 3



Compounds of Formula (4-4) (compounds of Formula (I) wherein R² is H and Cy is substituted piperazine) with a variety of substitution at positions R¹ and R²⁰ such as those described herein can be prepared, using a process as illustrated in **Scheme 4**. Compounds of Formula (1-4) can be converted to compounds of Formula (4-1) via a nucleophilic aromatic substitution (e.g., S_NAr) or a number of different cross-coupling reactions, including Buchwald-Hartwig amination, Cu-catalyzed amination and others. Selective deprotection of protecting group PG² (e.g., benzyl, Boc or SEM) generates compounds of Formula (4-2). Alternatively, compounds of Formula (4-2) can be prepared directly from compounds of Formula (1-4) by a nucleophilic aromatic substitution (e.g., S_NAr) or a number of different cross-coupling reactions, including Buchwald-Hartwig amination, Cu-catalyzed amination and others. Compounds of Formula (4-2) can be converted to compounds of Formula (4-3) via a substitution reaction or a cross-coupling reaction, including Buchwald-Hartwig amination, Cu-catalyzed amination and others. Deprotection of the protecting group, e.g. under acidic conditions, such as treatment with HCl or TFA, and/or under basic conditions such as treatment with aqueous ammonium hydroxide results in the formation of the desired compounds of Formula (4-4).

Scheme 4



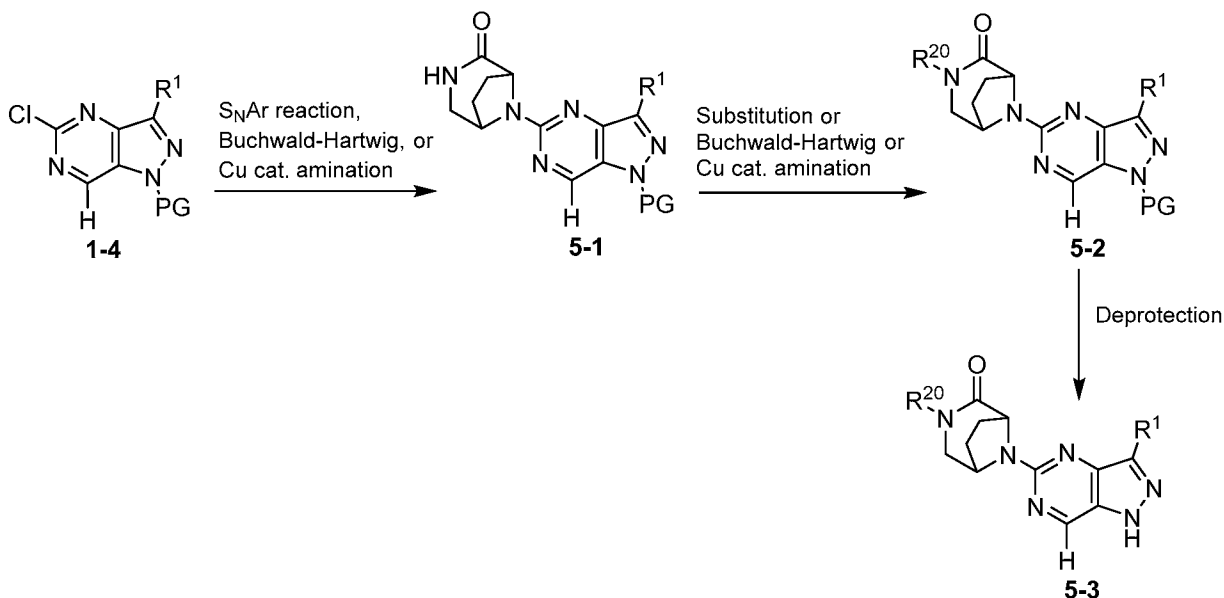
Compounds of Formula (5-3) (compounds of Formula (I) wherein R² is H and Cy is 3,8-diazabicyclo[3.2.1]octan-2-one) with a variety of substitution at positions R¹ and R²⁰ such

5 as those described herein can be prepared, using a process as illustrated in Scheme 5.

Compounds of Formula (1-4) can be converted to compounds of Formula (5-1) via a nucleophilic aromatic substitution (e.g., S_NAr) or a number of different cross-coupling reactions, including Buchwald-Hartwig amination, Cu-catalyzed amination and others.

Compounds of Formula (5-1) can be converted to compounds of Formula (5-2) via a
 10 substitution reaction or a cross-coupling reaction, including Buchwald-Hartwig amination, Cu-catalyzed amination and others. Deprotection of the protecting group, e.g. under acidic conditions, such as treatment with HCl or TFA, and/or under basic conditions such as treatment with aqueous ammonium hydroxide results in the formation of the desired compounds of Formula (5-3).

Scheme 5



Methods of Use

5 The present disclosure provides methods of modulating (e.g., inhibiting) ALK2 activity, said method comprising administering to a patient 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
 10 of the compounds of the disclosure, including any of the embodiments thereof, may be used.

In myelofibrosis (MF), a significant proportion of patients develop anemia and become dependent on frequent red blood cell (RBC) transfusions (Tefferi, A. et al. Mayo Clinic Proceedings 2012 87, 25-33). Elevated serum hepcidin levels in patients with MF have been shown to be associated with hemoglobin (Hb) levels, increased requirement for RBC
 15 transfusions and reduced survival (Pardanani, A. et al. American Journal of Hematology 2013, 88, 312-316). BMP signaling plays a central role in driving hepcidin transcriptional induction by activating SMAD signaling. In anemia mouse model, the liver-specific deletion of either ALK2 or ALK3 can block the induction of hepcidin production and iron overload (Steinbicker, A.U., et al. Blood 2011, 118, 4224-4230). Therefore, ALK2 inhibition could be
 20 useful in combination with ruxolitinib in the treatment of MF patients as the hepcidin-mediated FPN1 internalization and degradation may not require the action of JAK2 (Ross, S.L., et al. Cell Metabolism 2012, 15, 905-917). The ALK2 inhibition may block the

negative effect of hepcidin on iron metabolism and improve the anemia in MF patients (Asshoff, M. et al. Blood 2017, 129, 1823-1830).

Fibrodysplasia ossificans progressiva (FOP) is a human rare genetic bone disease and the patients were characterized by extraskeletal bone formation through endochondral ossification (Yu, P.B., et al. Nature Medicine 2008, 14, 1363-1369; Fukuda, T. et al. Journal of Biological Chemistry 2009 284, 7149-7156). 95% of FOP patients harbor point mutations in ACVR1/ALK2 and The responsive mutation for classic FOP is 617G >A (R206H) in the intracellular glycine and serine-rich (GS) domain of ALK2 (Shen, Q. et al. Journal of Clinical Investigation 2009, 119, 3462-3472). ALK2 mutations in atypical FOP patients have also been found in other amino acids of the GS domain or protein kinase domain (Fukuda, T. et al. Biochemical and Biophysical Research Communications 2008, 377, 905-909). The different ALK2 mutants have been shown to activate BMP signaling without exogenous BMP ligands constitutively and these ALK2 mutants can transmit much stronger BMP signaling upon ligand stimulation (Van Dinther, M. et al. Journal of Bone and Mineral Research 2010, 25, 1208-1215).

Activating mutations in ALK2 have also been identified in diffuse intrapontine gliomas (DIPG), which are highly aggressive glial neoplasms of the ventral pons in the pediatric population. ALK2 was reported as one of the most recurrently mutated gene in DIPG. ALK2 was found to carry nonsynonymous heterozygous somatic mutations in 46 of 195 (24%) cases at five specific residues. Patients with ALK2 mutations were predominantly female (approximately 2:1) and had a younger age of onset (approximately 5 years) and longer overall survival time (approximately 15 months) compared with wild-type IDPG. These ALK2 mutants are highly specific to DIPG and the ALK2 inhibitor LDN-19318917 results in significant inhibition of those ALK2 mutant DIPG cell viability (Taylor, K.R. et al. Nature Genetics 2014, 46, 457-461; Buczkowicz, P. et al. Nature Genetics 2014, 46, 451-456).

A method of treating a disease or disorder associated with inhibition of ALK2 activity can include administering to a patient in need thereof a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the disease or disorder is cancer. 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.

Compounds of the present disclosure can inhibit the activity of the FGFR enzyme. For example, compounds of the present disclosure can be used to inhibit activity of an FGFR enzyme in a cell or in an individual or patient in need of inhibition of the enzyme by administering an inhibiting amount of one or more compounds of the present disclosure to the cell, individual, or patient.

As FGFR inhibitors, the compounds of the present disclosure are useful in the treatment of various diseases associated with abnormal expression or activity of the FGFR enzyme or FGFR ligands. Compounds which inhibit FGFR will be useful in providing a means of preventing the growth or inducing apoptosis in tumors, particularly by inhibiting angiogenesis. It is therefore anticipated that compounds of the present disclosure will prove useful in treating or preventing proliferative disorders such as cancers. In particular, tumors with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the inhibitors.

In certain embodiments, the disclosure provides a method for treating a FGFR-mediated disorder in a patient in need thereof, comprising the step of administering to said patient a compound according to the invention, or a pharmaceutically acceptable composition thereof.

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.

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

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

Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (*e.g.*, primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL), multiple myeloma, cutaneous T-cell lymphoma, Waldenstrom's Macroglobulinemia, hairy cell lymphoma, chronic myelogenous lymphoma and Burkitt's lymphoma. Exemplary hematological cancers can also include 8p11 myeloproliferative syndrome. As used herein, the term "8p11 myeloproliferative syndrome" is meant to refer to myeloid/lymphoid neoplasms associated with eosinophilia and abnormalities of FGFR1.

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

Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung

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

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

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

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

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma),
25 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.

Exemplary nervous system cancers include cancers of the skull (osteoma,
30 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. Exemplary nervous system cancers also include neuro-ectodermal tumors and pineal tumors.

Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma). Exemplary gynecological cancers also include cancers of the breast (ductal carcinoma, lobular carcinoma, breast sarcoma, triple-negative breast cancer, HER2-positive breast cancer, inflammatory breast cancer, papillary carcinoma),

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.

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. Exemplary head and neck cancers also include tumors of the eye, tumors of the lips and mouth and squamous head and neck cancer.

The compounds of the present disclosure can also be useful in the inhibition of tumor metastases.

In some embodiments, compounds described herein can be used to treat Alzheimer's disease, HIV, or tuberculosis.

In some embodiments, the compounds provided herein may be used to treat tumors producing PGE2 (e.g. Cox-2 overexpressing tumors) and/or adenosine (CD73 and CD39 over-expressing 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.

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

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

 As used herein, the term "treating" or "treatment" refers to one or more of (1) inhibiting the disease; *e.g.*, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or
15 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.

20 As used herein, the term "contacting" refers to the bringing together of the indicated compounds in an in vitro system or an in vivo system such that they are in sufficient physical proximity to interact.

 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
25 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

30 One or more additional pharmaceutical agents or treatment methods such as, for example, anti-viral agents, chemotherapeutics or other anti-cancer agents, immune enhancers, immunosuppressants, radiation, anti-tumor and anti-viral vaccines, cytokine therapy (*e.g.*, IL2, GM-CSF, etc.), and/or tyrosine kinase inhibitors can be used in combination with compounds described herein for treatment of ALK2 and/or FGFR-

associated diseases, disorders or conditions, or diseases or conditions as described herein. The agents can be combined with the present compounds in a single dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

I. Immune-checkpoint therapies

5 In some embodiments, the compounds provided herein can be used in combination with one or more immune checkpoint inhibitors for the treatment of cancer as described herein. 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, CD28, CD39, CD40, CD122, CD96,
10 CD73, CD47, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137 (also known as 4-1BB), ICOS, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, TIGIT, 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
15 molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, TIGIT, and VISTA. In some embodiments, the compounds of the disclosure provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

20 In some embodiments, the compounds provided herein can be used in combination with one or more agonists of immune checkpoint molecules, e.g., OX40, CD27, GITR, and CD137 (also known as 4-1BB).

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

25 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), durvalumab (Imfinzi®), pidilizumab, SHR-1210, PDR001, MGA012, PDR001, AB122, or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In
30 some embodiments, the anti-PD1 antibody is pembrolizumab. In some embodiments, the anti-PD-1 monoclonal antibody is MGA012. In some embodiments, the anti-PD1 antibody is SHR-1210. Other anti-cancer agent(s) include antibody therapeutics such as 4-1BB (e.g. urelumab, utomilumab). In some embodiments, the anti-PD-1 monoclonal antibody is ipilumimab.

In some embodiments, the compounds of the disclosure can be used in combination with INCB086550.

In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-a small molecule PD-L1 antibody, or anti-CTLA-4 antibody.inhibitor. In some
5 embodiments, the small molecule PD-L1 inhibitor has an IC₅₀ less than 1 μM, less than 100 nM, less than 10 nM or less than 1 nM in a PD-L1 assay described in US Patent Publication Nos. US 20170107216, US 20170145025, US 20170174671, US 20170174679, US 20170320875, US 20170342060, US 20170362253, US 20180016260, US 20180057486, US 20180177784, US 20180177870, US 20180179179, US 20180179197, US 20180179201, and
10 US 20180179202, each of which is incorporated by reference in its entirety for all purposes.

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
15 MPDL3280A or MEDI4736.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1 and PD-L1, e.g., an anti-PD-1/PD-L1 monoclonal antibody. In some embodiments, the anti-PD-1/PD-L1 is MCLA-136.

In some embodiments, the inhibitor is MCLA-145.

20 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, tremelimumab, AGEN1884, or CP-675,206.

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
25 is IMC-CS4 or RG7155.

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, GSK2831781, or INCAGN2385.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor
30 of TIM3, e.g., an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is INCAGN2390, MBG453, or TSR-022.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is

TRX518, MK-4166, INCAGN1876, MK-1248, AMG228, BMS-986156, GWN323, or MEDI1873.

In some embodiments, the inhibitor of an immune checkpoint molecule is an agonist of OX40, e.g., OX40 agonist antibody or OX40L fusion protein. In some embodiments, the
5 anti-OX40 antibody is MEDI0562, MEDI6469, MOXR-0916, PF-04518600, GSK3174998, or BMS-986178. In some embodiments, the OX40L fusion protein is MEDI6383.

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.

10 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 β receptor.

In some embodiments, the compounds of the disclosure can be used in combination with one or more metabolic enzyme inhibitors. In some embodiments, the metabolic enzyme
15 inhibitor is an inhibitor of IDO1, TDO, or arginase. Examples of IDO1 inhibitors include epacadostat, NLG919, BMS-986205, PF-06840003, IOM2983, RG-70099 and LY338196. An example of an arginase inhibitor is CB-1158.

As provided throughout, the additional compounds, inhibitors, agents, etc. can be combined with the present compound in a single or continuous dosage form, or they can be
20 administered simultaneously or sequentially as separate dosage forms.

II. Cancer therapies

Cancer cell growth and survival can be impacted by multiple signaling pathways. Thus, it is useful to combine different enzyme/protein/receptor inhibitors, exhibiting different
25 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
30 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.

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

5 inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, TGF- β R, Pim, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IGF-1R, IR-R, PDGF α R, PDGF β R, CSF1R, 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,

10 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 additional FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, e.g., AZD4547,

15 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

20 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

25 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),

30 PARP (e.g., olaparib) and Pim kinases (LGH447, INCB053914 and SGI-1776) can also be combined with compounds of the present disclosure.

In some embodiments, compounds of the present disclosure can be combined with one or more JAK inhibitors (JAK1 and/or JAK2, e.g., ruxolitinib, baricitinib or INCB39110). In some embodiments, compounds of the present disclosure can be combined with one or

more JAK inhibitors (JAK1 and/or JAK2, e.g., ruxolitinib, baricitinib or INCB39110) for the treatment of cancers such as myeloproliferative diseases. For example, the myeloproliferative disease is myelofibrosis. In some embodiments, compounds of the present disclosure can be combined with ruxolitinib, or a pharmaceutically acceptable salt thereof. In some
5 embodiments, compounds of the present disclosure can be combined with ruxolitinib, or a pharmaceutically acceptable salt thereof, for the treatment of myeloproliferative disease such as myleofibrosis.

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
10 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 (CytosanTM), ifosfamide, melphalan, chlorambucil, pipobroman, triethylene-melamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine,
15 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).

The compounds of the present disclosure can further be used in combination with
20 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, CAR (Chimeric antigen receptor) T cell treatment as a booster for T cell activation, oncolytic
25 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, amsacrine, anastrozole, aphidicolon, arsenic trioxide, asparaginase,
30 axitinib, azacitidine, bevacizumab, bexarotene, baricitinib, bicalutamide, bleomycin, bortezomib, bortezomib, brivanib, buparlisib, busulfan intravenous, busulfan oral, calusterone, camptosar, capecitabine, carboplatin, carmustine, cediranib, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, crizotinib, cyclophosphamide, cytarabine, dacarbazine, dacomitinib, dactinomycin, dalteparin sodium, dasatinib, dactinomycin,

daunorubicin, decitabine, degarelix, denileukin, denileukin diftitox, deoxycoformycin, dexrazoxane, docetaxel, doxorubicin, droloxafine, dromostanolone propionate, eculizumab, enzalutamide, epidophyllotoxin, epirubicin, epothilones, 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, meclorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mithramycin, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, navelbene, necitumumab, nelarabine, neratinib, nilotinib, nilutamide, nofetumomab, oserelin, oxaliplatin, paclitaxel, pamidronate, panitumumab, pazopanib, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pilaralisib, pipobroman, plicamycin, ponatinib, porfimer, prednisone, procarbazine, quinacrine, ranibizumab, rasburicase, regorafenib, reloxafine, revlimid, rituximab, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, tegafur, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, triptorelin, uracil mustard, valrubicin, vandetanib, vinblastine, vincristine, vindesine, vinorelbine, vorinostat and zoledronate.

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

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.

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

The compounds of the present disclosure can further be used in combination with one or more anti-inflammatory agents, steroids, immunosuppressants or therapeutic antibodies. The steroids include but are not limited to 17 alpha-ethinylestradiol, diethylstilbestrol,

testosterone, prednisone, fluoxymesterone, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, and medroxyprogesteroneacetate.

The compounds of the present disclosure can also be used in combination with
5 lonafarnib (SCH6636), tipifarnib (R115777), L778123, BMS 214662, tezacitabine (MDL 101731), Sml1, triapine, didox, trimidox and amidox.

The compounds described herein 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
10 stimulating cytokines. Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MARTI and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

The compounds described herein can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to
15 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
20 compounds described herein can be combined with dendritic cells immunization to activate potent anti-tumor responses.

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

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

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

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

FD4 (also called beta-L-D4C and named beta-L-2', 3'-dicleoxy-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 Yisum Project No.11607.

The compounds described herein may be combined with or in sequence with other agents against membrane receptor kinases especially for patients who have developed primary or acquired resistance to the targeted therapy. These therapeutic agents include inhibitors or antibodies against EGFR, Her2, VEGFR, c-Met, Ret, IGFR1, or Flt-3 and against cancer-associated fusion protein kinases such as Bcr-Abl and EML4-Alk. Inhibitors against EGFR include gefitinib and erlotinib, and inhibitors against EGFR/Her2 include but are not limited to dacomitinib, afatinib, lapatinib and neratinib. Antibodies against the EGFR include but are not limited to cetuximab, panitumumab and necitumumab. Inhibitors of c-Met may be used in combination with compound disclosed herein. These include onartumzumab, tivantinib, and INC-280. Agents against Abl (or Bcr-Abl) include imatinib, dasatinib, nilotinib, and ponatinib and those against Alk (or EML4-ALK) include crizotinib.

Angiogenesis inhibitors may be efficacious in some tumors in combination with compounds disclosed herein. These include antibodies against VEGF or VEGFR or kinase inhibitors of VEGFR. Antibodies or other therapeutic proteins against VEGF include bevacizumab and aflibercept. Inhibitors of VEGFR kinases and other anti-angiogenesis inhibitors include but are not limited to sunitinib, sorafenib, axitinib, cediranib, pazopanib, regorafenib, brivanib, and vandetanib.

Activation of intracellular signaling pathways is frequent in cancer, and agents targeting components of these pathways have been combined with receptor targeting agents to enhance efficacy and reduce resistance. Examples of agents that may be combined with compounds described herein include inhibitors of the PI3K-AKT-mTOR pathway, inhibitors of the Raf-MAPK pathway, inhibitors of JAK-STAT pathway, and inhibitors of protein chaperones and cell cycle progression.

Agents against the PI3 kinase include but are not limited topilaralisib, idelalisib, buparlisib. Inhibitors of mTOR such as rapamycin, sirolimus, temsirolimus, and everolimus

may be combined with compounds of the invention. Other suitable examples include but are not limited to vemurafenib and dabrafenib (Raf inhibitors) and trametinib, selumetinib and GDC-0973 (MEK inhibitors). Inhibitors of one or more JAKs (e.g., ruxolitinib, baricitinib, tofacitinib), Hsp90 (e.g., tanespimycin), cyclin dependent kinases (e.g., palbociclib), HDACs (e.g., panobinostat), PARP (e.g., olaparib), and proteasomes (e.g., bortezomib, carfilzomib) can also be combined with compounds described herein. In some embodiments, the JAK inhibitor is selective for JAK1 over JAK2 and JAK3.

Other suitable agents for use in combination with compounds described herein include chemotherapy combinations such as platinum-based doublets used in lung cancer and other solid tumors (cisplatin or carboplatin plus gemcitabine; cisplatin or carboplatin plus docetaxel; cisplatin or carboplatin plus paclitaxel; cisplatin or carboplatin plus pemetrexed) or gemcitabine plus paclitaxel bound particles (Abraxane®).

Suitable chemotherapeutic or other anti-cancer agents include, for example, alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes) such as uracil mustard, chlormethine, cyclophosphamide (CytosanTM), ifosfamide, melphalan, chlorambucil, pipobroman, triethylene-melamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, and temozolomide.

Other suitable agents for use in combination with compounds described herein include steroids including 17 alpha-ethinylestradiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, and medroxyprogesteroneacetate.

Other suitable agents for use in combination with compounds described herein include: dacarbazine (DTIC), optionally, along with other chemotherapy drugs such as carmustine (BCNU) and cisplatin; the "Dartmouth regimen," which consists of DTIC, BCNU, cisplatin and tamoxifen; a combination of cisplatin, vinblastine, and DTIC; or temozolomide. Compounds described herein may also be combined with immunotherapy drugs, including cytokines such as interferon alpha, interleukin 2, and tumor necrosis factor (TNF) in.

Suitable chemotherapeutic or other anti-cancer agents include, for example, antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) such as methotrexate, 5-fluorouracil,

floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, and gemcitabine.

Suitable chemotherapeutic or other anti-cancer agents further include, for example, certain natural products and their derivatives (for example, vinca alkaloids, antitumor
5 antibiotics, enzymes, lymphokines and epipodophyllotoxins) such as vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (TAXOLTM), mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, interferons (especially IFN- α), etoposide, and teniposide.

Other cytotoxic agents include navelbene, CPT-11, anastrozole, letrozole,
10 capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine.

Also suitable are cytotoxic agents such as epipodophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth
inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth
15 factors.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4, 4-1BB, PD-L1 and PD-1 antibodies, or antibodies to cytokines (IL-10, TGF- β , etc.).

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

Other anti-cancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer.

Anti-cancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses. In some embodiments, tumor vaccines include the proteins from viruses
25 implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). 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.

30 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.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic

agents is described in the "Physicians' Desk Reference" (PDR, e.g., 1996 edition, Medical Economics Company, Montvale, NJ), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

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

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. The pharmaceutical compositions can comprise of a compound described herein and one or more second therapeutic agents as described herein. For example, the second therapeutic agent is a JAK inhibitor such as ruxolitinib. The compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is indicated and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, e.g., by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the present disclosure or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an

excipient, diluted by an excipient or enclosed within such a carrier in the form of, *e.g.*, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, *e.g.*, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

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

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

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

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

In some embodiments, the composition is a sustained release composition comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at

least one pharmaceutically acceptable carrier or excipient. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose and polyethylene oxide. In some
5 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
10 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™).
15 In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (*e.g.*, Polyox WSR 1105™).

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

The compositions can be formulated in a unit dosage form, each dosage containing
20 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
25 subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

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

may be sterile and/or substantially isotonic and/or in full compliance with all Good Manufacturing Practice regulations of the U.S. Food and Drug Administration.

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

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

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

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the

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

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

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

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

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

The compositions administered to a patient can be in the form of pharmaceutical
10 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
15 understood that use of certain of the foregoing excipients, carriers or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, *e.g.*, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing
20 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
25 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
30 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

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 ALK2 protein and/or FGFR protein in tissue samples, including human, and for identifying ALK2 ligands and/or FGFR ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes ALK2 binding assays that contain such labeled compounds and FGFR binding assays that contain such labeled compounds.

The present invention further includes isotopically-substituted compounds of the disclosure. An "isotopically-substituted" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having the same atomic number but 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., ^2H and ^{13}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., ^3H and ^{14}C . Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I and ^{131}I . The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. In some embodiments, the radionuclide is selected from the group consisting of ^3H , ^{14}C , ^{125}I , ^{35}S and ^{82}Br . For *in vitro* ALK2 labeling and competition assays, compounds that incorporate ^3H , ^{14}C , ^{82}Br , ^{125}I , ^{131}I , or ^{35}S will generally be most useful. For radio-imaging applications ^{11}C , ^{18}F , ^{125}I , ^{123}I , ^{124}I , ^{131}I , ^{75}Br , ^{76}Br or ^{77}Br will generally be most useful. The present disclosure can further include synthetic methods for incorporating radio-isotopes into compounds of the disclosure. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of disclosure.

One or more constituent atoms of the compounds presented herein 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. In some embodiments, the

compound includes two or more deuterium atoms. In some embodiments, the compound includes 1-2, 1-3, 1-4, 1-5, or 1-6 deuterium atoms. In some embodiments, all of the hydrogen atoms in a compound can be replaced or substituted by 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; The Organic Chemistry of Isotopic Labelling by James R. Hanson, Royal Society of Chemistry, 2011). Isotopically labeled compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

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. (see *e.g.*, A. Kerekes et. al. *J. Med. Chem.* 2011, 54, 201-210; R. Xu et. al. *J. Label Compd. Radiopharm.* 2015, 58, 308-312). In particular, substitution at one or more metabolism sites may afford one or more of the therapeutic advantages. 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 ALK2 protein or FGFR protein by monitoring its concentration variation when contacting with the ALK2 protein or FGFR protein, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to a ALK2 protein or FGFR protein (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the ALK2 protein or FGFR 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

The present disclosure also includes pharmaceutical kits useful, *e.g.*, in the treatment or prevention of diseases or disorders associated with the activity of ALK2 and/or FGFR, such as cancer or infections, which include one or more containers containing a

pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, *e.g.*, containers with one or more pharmaceutically acceptable carriers, additional containers, *etc.*, as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to inhibit the activity of ALK2 and/or FGFR according to at least one assay described herein.

EXAMPLES

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. Combi. Chem.*, 4, 295 (2002); "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", K. Blom, R. Sparks, J. Doughty, G. Everlof, T. Haque, A. Combs, *J. Combi. Chem.*, 5, 670 (2003); and "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Combi. 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™ C₁₈ 5 µm particle size, 2.1 x 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.

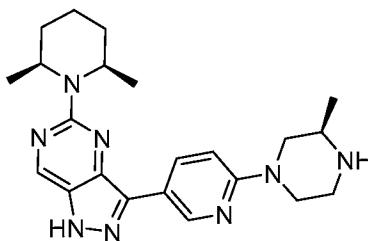
Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-

phase high performance liquid chromatography (RP-HPLC) column conditions are as follows:

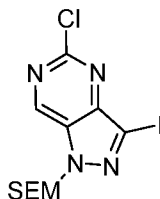
pH = 2 purifications: Waters Sunfire™ C₁₈ 5 μm particle size, 19 x 100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific 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 x 100 mm column was 60 mL/minute.

pH = 10 purifications: Waters XBridge C₁₈ 5 μm particle size, 19 x 100 mm column, eluting with mobile phase A: 0.15% NH₄OH 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 x 100 mm column was 60 mL/minute.

Example 1. 5-((2*R*,6*S*)-2,6-Dimethylpiperidin-1-yl)-3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine



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

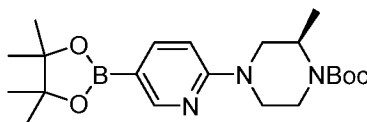


To a solution of 5-chloro-1*H*-pyrazolo[4,3-*d*]pyrimidine (9.8 g, 63.4 mmol) in DMF (100 mL) was added *N*-iodosuccinimide (15.69 g, 69.7 mmol) and the resulting solution was heated to 50 °C. After 2 hrs, the reaction mixture was cooled to r.t., diluted with EtOAc and water. The organic layer was washed with brine, dried with MgSO₄, filtered and

concentrated.

The crude was taken up in 100 mL DMF and NaH (2.79 g, 69.7 mmol, 60% dispersion in mineral oil) was added at 0 °C. The mixture was stirred at r.t. for 10 min then 2-(trimethylsilyl)ethoxymethyl chloride (12.37 mL, 69.7 mmol) was added. The resulting mixture was stirred at r.t.. After 1 hr, the reaction mixture was diluted with EtOAc and water. The organic layer was washed with brine, dried with MgSO₄, filtered and concentrated. The crude was then purified by CombiFlash Rf+ Lumen. LCMS calculated for C₁₁H₁₇ClIN₄OSi (M+H)⁺: m/z = 411.0; found 411.1.

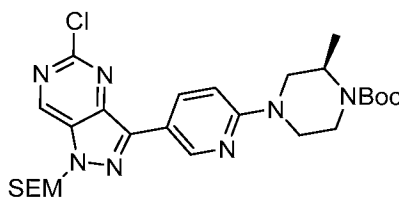
- 10 *Step 2. tert-Butyl (R)-2-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate*



- 15 A mixture of *tert*-butyl (*R*)-4-(5-bromopyridin-2-yl)-2-methylpiperazine-1-carboxylate (1.84 g, 5.16 mmol), bis(pinacolato)diboron (1.836 g, 7.23 mmol), potassium acetate (1.521 g, 15.49 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.422 g, 0.516 mmol) in dioxane (25.8 mL) under N₂ was heated to 85 °C.

- 20 After 16 hrs, the reaction mixture was cooled to r.t., quenched with water and EtOAc, and filtered through celite. The organic layer was washed with brine, dried with MgSO₄, filtered and concentrated. The crude was then purified by CombiFlash Rf+ Lumen. LCMS calculated for C₁₅H₂₅BN₃O₄ (M-C₆H₉)⁺: m/z = 322.2; found 322.2.

Step 3. tert-Butyl (R)-4-(5-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate



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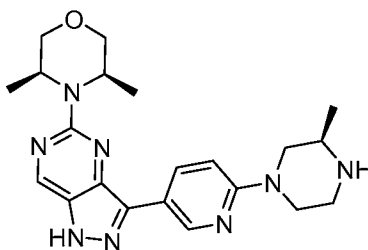
A mixture of 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (2.444 g, 5.95 mmol), *tert*-butyl (*R*)-2-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate (2.00 g, 4.96 mmol), potassium

carbonate (2.056 g, 14.88 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (1.215 g, 1.488 mmol) in dioxane (39.7 mL) and water (9.92 mL) was heated to 90 °C under N₂. After 20 hrs, the reaction mixture was cooled to r.t., quenched with water and EtOAc, then filtered through celite. The organic layer was washed with brine, dried with MgSO₄ and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₂₆H₃₉ClN₇O₃Si (M+H)⁺: m/z = 560.3; found 560.3.

Step 4. 5-((2R,6S)-2,6-Dimethylpiperidin-1-yl)-3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine

A solution of *tert*-butyl (R)-4-(5-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (38 mg, 0.068 mmol), *N,N*-diisopropylethylamine (0.059 mL, 0.339 mmol) and *cis*-2,6-dimethylpiperidine (0.046 mL, 0.339 mmol) in 1-methyl-2-pyrrolidinone (1 mL) was heated to 120 °C. After 4 days, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL DCM and 1 mL TFA and stirred at r.t. for 2 hrs. The solvent was then removed under vacuum. The crude was then taken up in 1 mL MeOH and 0.7 mL NH₄OH (aq) was added. The resulting mixture was stirred at r.t. for 5 min 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 C₂₂H₃₁N₈ (M+H)⁺: m/z = 407.3; found 407.3. The product was isolated as the TFA salt.

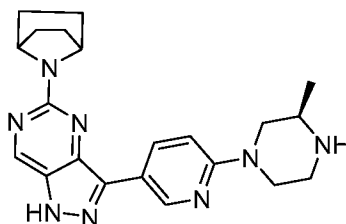
Example 2. (3R,5S)-3,5-Dimethyl-4-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)morpholine



This compound was prepared according to the procedures described in Example 1, using *cis*-3,5-dimethylmorpholine instead of *cis*-2,6-dimethylpiperidine as starting material.

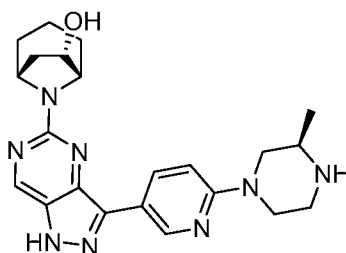
LCMS calculated for $C_{21}H_{29}N_8O$ ($M+H$)⁺: m/z = 409.2; found: 409.3. The product was isolated as the TFA salt.

5 **Example 3. 5-(7-Azabicyclo[2.2.1]heptan-7-yl)-3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine**



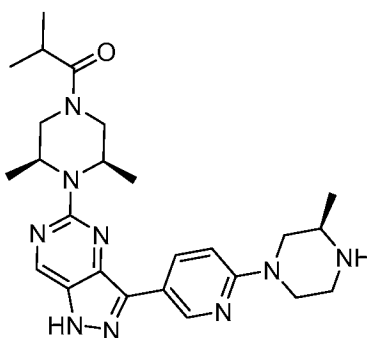
This compound was prepared according to the procedures described in Example 1, using 7-azabicyclo[2.2.1]heptane instead of *cis*-2,6-dimethylpiperidine as starting material. LCMS calculated for $C_{21}H_{27}N_8$ ($M+H$)⁺: m/z = 391.2; found: 391.3. The product was isolated as the TFA salt.

10 **Example 4. (1*R*,5*S*,6*S*)-8-(3-(6-((*R*)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-6-ol**

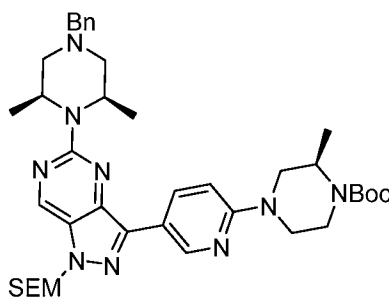


15 This compound was prepared according to the procedures described in Example 1, using (1*R*,5*S*,6*S*)-8-azabicyclo[3.2.1]octan-6-ol instead of *cis*-2,6-dimethylpiperidine as starting material. LCMS calculated for $C_{22}H_{29}N_8O$ ($M+H$)⁺: m/z = 421.2; found: 421.2. The product was isolated as the TFA salt.

20 **Example 5. 1-((3*R*,5*S*)-3,5-Dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)-2-methylpropan-1-one**



Step 1. *tert*-Butyl (R)-4-(5-(5-((2R,6S)-4-benzyl-2,6-dimethylpiperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate

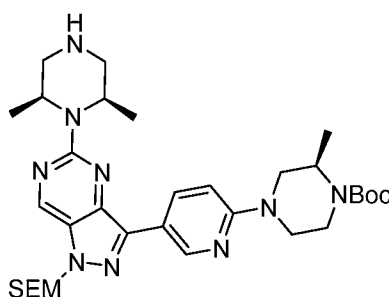


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To a microwave vial was added *tert*-butyl (R)-4-(5-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (380 mg, 0.678 mmol, see Example 1, Step 3), 1-benzyl-*cis*-3,5-dimethylpiperazine (770 mg, 3.77 mmol) and *N,N*-diisopropylethylamine (1.185 mL, 6.78 mmol) in 1-methyl-2-pyrrolidinone (3 mL). The reaction mixture was heated to 150 °C under microwave for 42 hrs.

The reaction was then cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄, filtered and concentrated. The crude residue was taken up in 2 mL DCM and *N,N*-diisopropylethylamine (1.185 mL, 6.78 mmol) and di-*tert*-butyl dicarbonate (0.315 mL, 1.357 mmol) was added. The mixture was stirred at r.t. for 2 hrs. The reaction was then quenched with water, extracted with DCM, washed with brine and dried with Na₂SO₄. The crude was purified by CombiFlash Rf+ Lumen. LCMS calculated for C₃₉H₅₈N₉O₅Si (M+H)⁺: m/z = 728.4; found 728.5.

Step 2. *tert*-Butyl (R)-4-(5-(5-((2R,6S)-2,6-Dimethylpiperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate

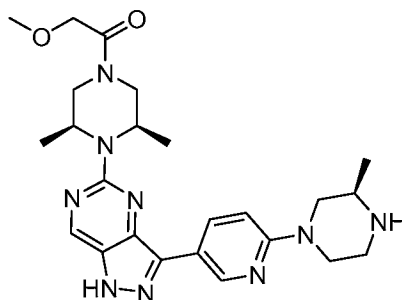


A mixture of *tert*-butyl (*R*)-4-(5-(5-((2*R*,6*S*)-4-benzyl-2,6-dimethylpiperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (108 mg, 0.148 mmol), palladium on carbon (10%, 23.7 mg, 0.022 mmol) and ammonium formate (94 mg, 1.483 mmol) was taken up in methanol (2 mL) under N₂ and heated to 60 °C. After 22 hrs, the reaction mixture was cooled to r.t., diluted with EtOAc, filtered through celite, and concentrated *in vacuo*. The obtained crude product was used in the next step without further purification. LCMS calculated for C₃₂H₅₂N₉O₃Si (M+H)⁺: m/z = 638.4; found 638.5.

Step 3. 1-((3R,5S)-3,5-Dimethyl-4-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-1-yl)-2-methylpropan-1-one

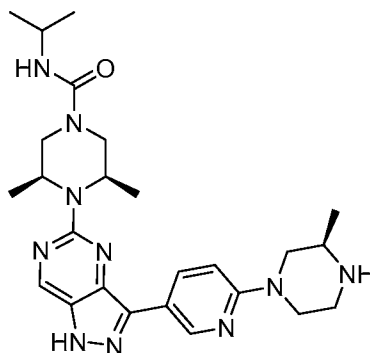
A solution of *tert*-butyl (*R*)-4-(5-(5-((*2R,6S*)-2,6-dimethylpiperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (14 mg, 0.022 mmol) in 0.5 mL DCM was added triethylamine (0.012 mL, 0.088 mmol) and isobutyryl chloride (4.60 μ L, 0.044 mmol). The reaction mixture was stirred at r.t. for 18 hrs. The reaction was then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL DCM and 1 mL TFA and stirred at r.t. for 2 hrs. The solvent was then removed *in vacuo*. The crude was then taken up in 1 mL MeOH and 0.7 mL NH₄OH (aq) was added. The resulting mixture was stirred at r.t. for 5 min 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 C₂₅H₃₆N₉O (M+H)⁺: *m/z* = 478.3; found 478.3. ¹H NMR (600 MHz, DMSO) δ 13.47 (s, 1H), 9.43 (s, 1H), 9.21 (d, *J* = 2.3 Hz, 1H), 9.07 (s, 1H), 8.46 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 1H), 4.86 (m, 2H), 4.47 – 4.37 (m, 3H), 4.03 (m, 1H), 3.48 – 3.27 (m, 4H), 3.25 – 2.85 (m, 4H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.27 – 1.13 (m, 6H), 1.1 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H) ppm. The product was isolated as the TFA salt.

Example 6. 1-((3*R*,5*S*)-3,5-Dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)-2-methoxyethan-1-one



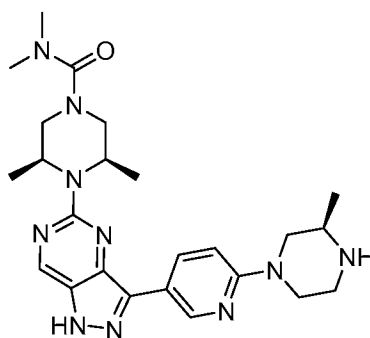
This compound was prepared according to the procedures described in Example 5, using 2-methoxyacetyl chloride instead of isobutyryl chloride as starting material. LCMS calculated for $C_{24}H_{34}N_9O_2$ ($M+H$)⁺: m/z = 480.3; found: 480.3. The product was isolated as the TFA salt.

Example 7. (3*R*,5*S*)-*N*-isopropyl-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxamide



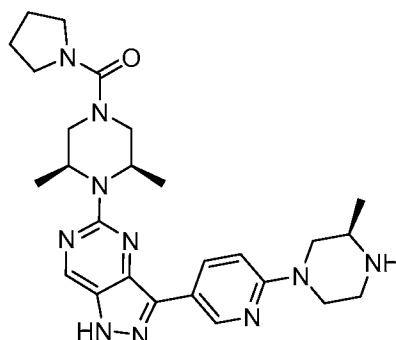
This compound was prepared according to the procedures described in Example 5, using isopropyl isocyanate instead of isobutyryl chloride as starting material. LCMS calculated for $C_{25}H_{37}N_{10}O$ ($M+H$)⁺: m/z = 493.3; found: 493.4. The product was isolated as the TFA salt.

Example 8. (3*R*,5*S*)-*N,N*,3,5-tetramethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxamide

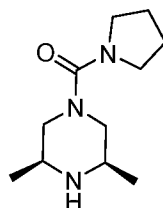


This compound was prepared according to the procedures described in Example 5, using dimethylcarbamoyl chloride instead of isobutyryl chloride as starting material. LCMS calculated for $C_{24}H_{35}N_{10}O$ ($M+H$)⁺: m/z = 479.3; found: 479.4. 1H NMR (600 MHz, DMSO) δ 13.41 (s, 1H), 9.31 (s, 1H), 9.21 (d, J = 2.2 Hz, 1H), 9.07 (s, 1H), 8.47 (dd, J = 8.9, 2.4 Hz, 1H), 7.11 (m, 1H), 4.83 (m, 2H), 4.43 (m, 2H), 3.56 (d, J = 12.6 Hz, 2H), 3.44 – 3.05 (m, 4H), 3.01 – 2.92 (m, 3H), 2.87 (s, 6H), 1.33 (d, J = 6.8 Hz, 6H), 1.30 (d, J = 6.6 Hz, 3H) ppm. The product was isolated as the TFA salt.

Example 9. ((3*R*,5*S*)-3,5-Dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone



*Step 1. ((3*R*,5*S*)-3,5-Dimethylpiperazin-1-yl)(pyrrolidin-1-yl)methanone*



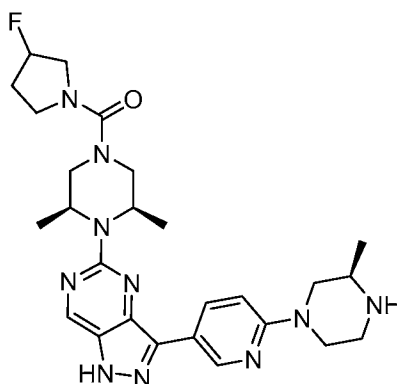
To a solution of *cis*-2,6-dimethylpiperazine (0.057 g, 0.5 mmol) in 2.5 mL DCM was added pyrrolidine-1-carbonyl chloride (0.066 mL, 0.600 mmol). The resulting solution was stirred at r.t. for 16 hrs. The reaction was then quenched with water, extracted with EtOAc, washed with brine and dried with Na_2SO_4 . The obtained crude product was used in the next

step without further purification. LCMS calculated for $C_{11}H_{22}N_3O$ ($M+H$)⁺: m/z = 212.2; found 212.2.

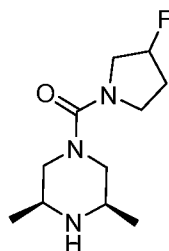
Step 2. ((3R,5S)-3,5-Dimethyl-4-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone

A solution of *tert*-butyl (*R*)-4-(5-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-*d*]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (30 mg, 0.054 mmol, see Example 1, *Step 3*), ((3*R*,5*S*)-3,5-dimethylpiperazin-1-yl)(pyrrolidin-1-yl)methanone (106 mg, 0.5 mmol), *N,N*-diisopropylethylamine (0.2 mL, 1.145 mmol) in 1-methyl-2-pyrrolidinone (1 mL) was heated to 120 °C. After 5 days, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL DCM and 1 mL TFA and stirred at r.t. for 2 hrs. The solvent was then removed *in vacuo*. The crude was then taken up in 1 mL MeOH and 0.7 mL NH₄OH (aq) was added. The resulting mixture was stirred at r.t. for 5 min 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 $C_{26}H_{37}N_{10}O$ ($M+H$)⁺: m/z = 505.3; found 505.5. The product was isolated as the TFA salt.

Example 10. ((3*R*,5*S*)-3,5-Dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)(3-fluoropyrrolidin-1-yl)methanone



Step 1. ((3R,5S)-3,5-Dimethylpiperazin-1-yl)(3-fluoropyrrolidin-1-yl)methanone

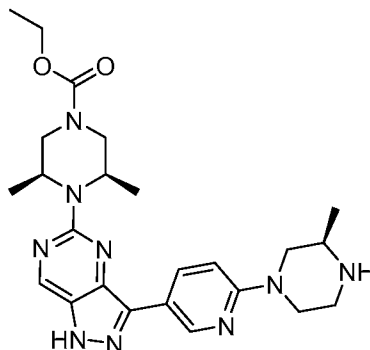


To a solution of 3-fluoropyrrolidine hydrochloride (0.104 g, 0.825 mmol) and *N,N*-diisopropylethylamine (0.437 mL, 2.500 mmol) in 3 mL DCM was added triphosgene (0.074 g, 0.25 mmol) in 0.5 mL DCM and the resulting mixture was stirred at r.t. After 4 hrs, *N,N*-diisopropylethylamine (0.437 mL, 2.500 mmol) and *cis*-2,6-dimethylpiperazine (0.057 g, 0.500 mmol) was added and the resulting mixture was stirred at r.t. After 20 hrs, the reaction was quenched with water, extracted with DCM, washed with brine and dried with Na₂SO₄. The obtained crude product was used in the next step without further purification. LCMS calculated for C₁₁H₂₁FN₃O (M+H)⁺: m/z = 230.2; found 230.3.

Step 2. ((3R,5S)-3,5-Dimethyl-4-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-1-yl)(3-fluoropyrrolidin-1-yl)methanone

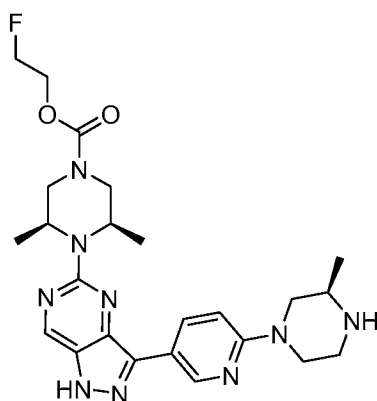
This compound was prepared according to the procedures described in Example 9, using ((3R,5S)-3,5-dimethylpiperazin-1-yl)(3-fluoropyrrolidin-1-yl)methanone instead of ((3R,5S)-3,5-dimethylpiperazin-1-yl)(pyrrolidin-1-yl)methanone as starting material. LCMS calculated for C₂₆H₃₆FN₁₀O (M+H)⁺: m/z = 523.3; found: 523.5. The product was isolated as the TFA salt.

Example 11. Ethyl (3R,5S)-3,5-dimethyl-4-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate



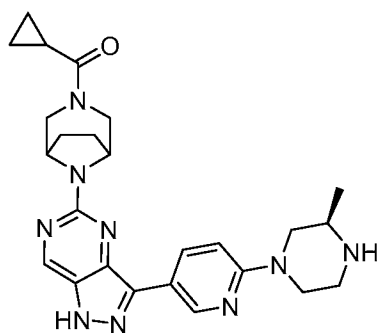
This compound was prepared according to the procedures described in Example 9, using ethyl chloroformate instead of pyrrolidine-1-carbonyl chloride as starting material. LCMS calculated for C₂₄H₃₄N₉O₂ (M+H)⁺: m/z = 480.3; found: 480.3. The product was isolated as the TFA salt.

Example 12. 2-Fluoroethyl (3R,5S)-3,5-dimethyl-4-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate

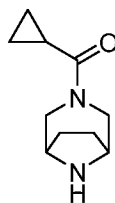


This compound was prepared according to the procedures described in Example 9, using 2-fluoroethyl chloroformate instead of pyrrolidine-1-carbonyl chloride as starting material. LCMS calculated for $C_{24}H_{33}FN_9O_2$ ($M+H$)⁺: m/z = 498.3; found: 498.3. The product was isolated as the TFA salt.

Example 13. Cyclopropyl((1R,5S)-8-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)methanone



Step 1. ((1R,5S)-3,8-Diazabicyclo[3.2.1]octan-3-yl)(cyclopropyl)methanone



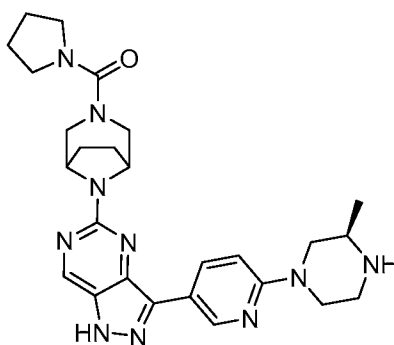
To a solution of *tert*-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.471 mmol) in 2.4 mL DCM was added triethylamine (263 μ L, 1.884 mmol) and cyclopropanecarbonyl chloride (85 μ L, 0.942 mmol) and the resulting solution was stirred at r.t. After 20 hrs, the reaction was quenched with water, extracted with DCM, washed with brine and dried with Na_2SO_4 . The crude was taken up in 1 mL DCM and 1 mL TFA was added. The reaction mixture was stirred at r.t. After 1 hr, the solvent was removed *in vacuo*. The obtained crude product was used in the next step without further purification. LCMS

calculated for $C_{10}H_{17}N_2O$ ($M+H$)⁺: $m/z = 181.1$; found 181.1.

Step 2. Cyclopropyl((1R,5S)-8-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)methanone

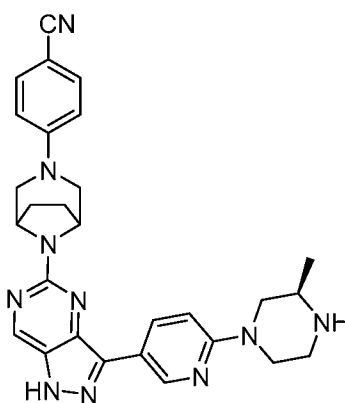
This compound was prepared according to the procedures described in Example 9, using ((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)(cyclopropyl)methanone instead of ((3R,5S)-3,5-dimethylpiperazin-1-yl)(pyrrolidin-1-yl)methanone as starting material. LCMS calculated for $C_{25}H_{32}N_9O$ ($M+H$)⁺: $m/z = 474.3$; found: 474.3. The product was isolated as the TFA salt.

Example 14. ((1R,5S)-8-(3-(6-((R)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)(pyrrolidin-1-yl)methanone

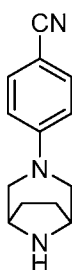


This compound was prepared according to the procedures described in Example 13, using pyrrolidine-1-carbonyl chloride instead of cyclopropanecarbonyl chloride as starting material. LCMS calculated for $C_{26}H_{35}N_{10}O$ ($M+H$)⁺: $m/z = 503.3$; found: 503.3. ¹H NMR (600 MHz, DMSO) δ 13.46 (s, 1H), 9.19 (d, $J = 2.2$ Hz, 1H), 9.06 (s, 1H), 8.87 (s, 1H), 8.46 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.13 (d, $J = 9.0$ Hz, 1H), 4.79 (m, 2H), 4.49 – 4.35 (m, 2H), 3.60 (dd, $J = 12.5, 2.4$ Hz, 2H), 3.46 – 3.30 (m, 2H), 3.28 – 3.20 (m, 4H), 3.20 – 3.05 (m, 4H), 3.01 – 2.93 (dd, $J = 13.8, 10.7$ Hz, 1H), 1.95 – 1.83 (m, 4H), 1.76 – 1.69 (m, 4H), 1.30 (d, $J = 6.4$ Hz, 3H) ppm. The product was isolated as the TFA salt.

Example 15. 4-((1R,5S)-8-(3-(6-((R)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)benzonitrile



Step 1. 4-((1R,5S)-3,8-Diazabicyclo[3.2.1]octan-3-yl)benzonitrile

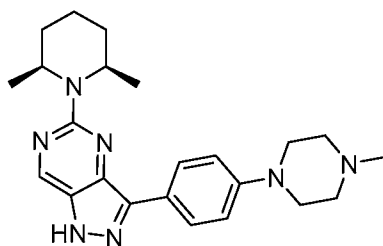


A mixture of *tert*-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.471 mmol), 4-bromobenzonitrile (129 mg, 0.707 mmol), sodium *tert*-butoxide (67.9 mg, 0.707 mmol), RuPhos Pd G3 (19.70 mg, 0.024 mmol) and RuPhos (11.0 mg, 0.024 mmol) in 2.4 mL THF was heated to 80 °C. After 16 hrs, the reaction was diluted with EtOAc, filtered through celite, and concentrated. The crude was purified by CombiFlash Rf+ Lumen. The obtained product was then taken up in 1 mL DCM and 1 mL TFA was added. The reaction mixture was stirred at r.t. After 1 hr, the solvent was removed *in vacuo*. The obtained crude product was used in the next step without further purification.

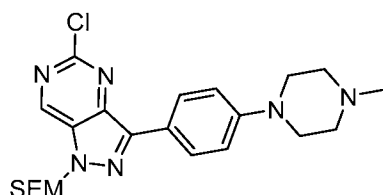
Step 2. 4-((1R,5S)-8-(3-(6-((R)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)benzonitrile

This compound was prepared according to the procedures described in Example 9, using 4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)benzonitrile instead of ((3R,5S)-3,5-dimethylpiperazin-1-yl)(pyrrolidin-1-yl)methanone as starting material. LCMS calculated for C₂₈H₃₁N₁₀ (M+H)⁺: m/z = 507.3; found: 507.3. The product was isolated as the TFA salt.

Example 16. 5-((2R,6S)-2,6-Dimethylpiperidin-1-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine



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



5 This compound was prepared according to the procedures described in Example 1, Step 3, using (4-(4-methylpiperazin-1-yl)phenyl)boronic acid instead of *tert*-butyl (*R*)-2-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate as starting material. LCMS calculated for C₂₂H₃₂ClN₆OSi (M+H)⁺: m/z = 459.2; found: 459.3.

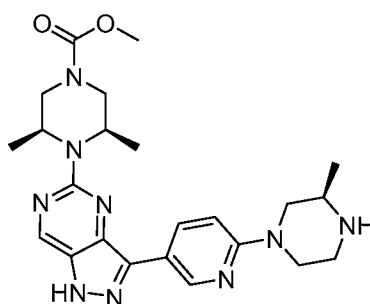
10

Step 2. 5-((2*R*,6*S*)-2,6-Dimethylpiperidin-1-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidine

This compound was prepared according to the procedures described in Example 1, Step 4, using 5-chloro-3-(4-(4-methylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine instead of *tert*-butyl (*R*)-4-(5-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate as starting material. LCMS calculated for C₂₃H₃₂N₇ (M+H)⁺: m/z = 406.3; found: 406.3. The product was isolated as the TFA salt.

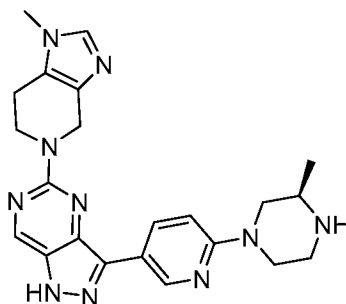
15

20 **Example 17. Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate**



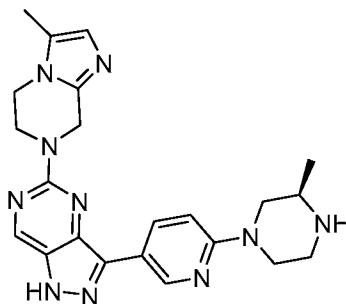
This compound was prepared according to the procedures described in Example 9, using methyl chloroformate instead of pyrrolidine-1-carbonyl chloride as starting material. LCMS calculated for $C_{23}H_{32}N_9O_2$ ($M+H$)⁺: m/z = 466.3; found: 466.1. The product was isolated as the TFA salt.

Example 18. (R)-5-(1-Methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)-3-(6-(3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine



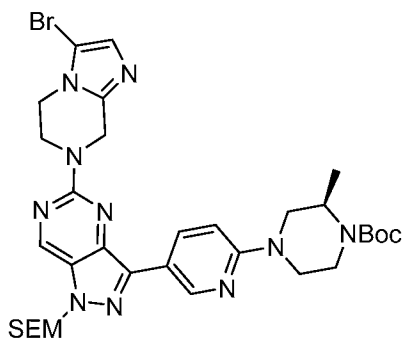
This compound was prepared according to the procedures described in Example 1, using 1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine instead of *cis*-2,6-dimethylpiperidine as starting material. LCMS calculated for $C_{22}H_{27}N_{10}$ ($M+H$)⁺: m/z = 431.2; found: 431.1. The product was isolated as the TFA salt.

Example 19. (R)-5-(3-Methyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-3-(6-(3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine



Step 1. tert-Butyl (R)-4-(5-(5-(3-bromo-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-1-((2-

(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate

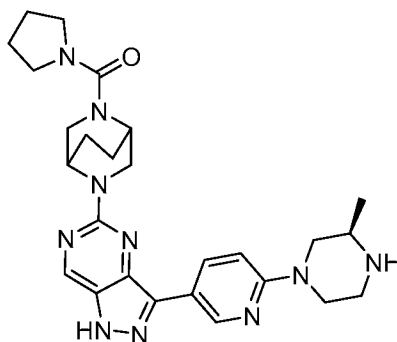


A solution of *tert*-butyl (*R*)-4-(5-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (100 mg, 0.179 mmol, see Example 1, *Step* 3), 3-bromo-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (108 mg, 0.536 mmol), and *N,N*-diisopropylethylamine (0.280 mL, 1.607 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was combined and heated to 120 °C. After 3 days, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was then purified by CombiFlash Rf+ Lumen. LCMS calculated for C₃₂H₄₆BrN₁₀O₃Si (M-C₆H₉)⁺: *m/z* = 725.3; found 725.4.

*Step 2. (R)-5-(3-Methyl-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-3-(6-(3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine*

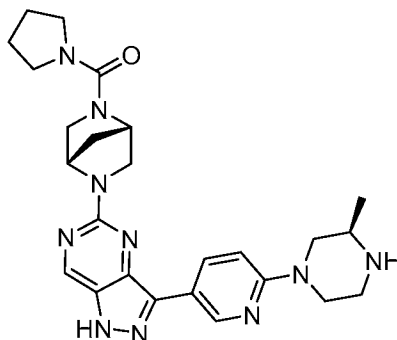
A solution of *tert*-butyl (*R*)-4-(5-(5-(3-bromo-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)pyridin-2-yl)-2-methylpiperazine-1-carboxylate (20 mg, 0.028 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (17.30 mg, 0.138 mmol), XPhos Pd G2 (4.34 mg, 5.51 μmol), and potassium phosphate (23.40 mg, 0.110 mmol) in dioxane (1 mL) and water (0.1 mL) was heated to 75 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 1 mL HCl (4 M solution in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₂₂H₂₇N₁₀ (M+H)⁺: *m/z* = 431.2; found 431.4. The product was isolated as the TFA salt.

Example 20. (5-(3-(6-((*R*)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-

***d*]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)(pyrrolidin-1-yl)methanone**

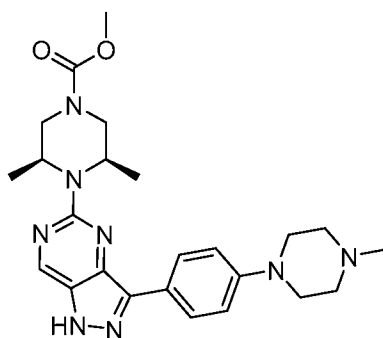
This compound was prepared according to the procedures described in Example 14, using *tert*-butyl 2,5-diazabicyclo[2.2.2]octane-2-carboxylate instead of *tert*-butyl (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate as starting material. LCMS calculated for C₂₆H₃₅N₁₀O (M+H)⁺: *m/z* = 503.3; found: 503.2. The product was isolated as the TFA salt.

Example 21. ((1*S*,4*S*)-5-(3-(6-((*R*)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)(pyrrolidin-1-yl)methanone

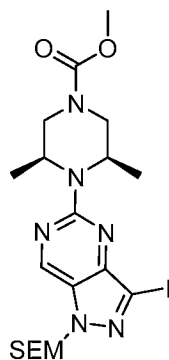


This compound was prepared according to the procedures described in Example 14, using *tert*-butyl (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate instead of *tert*-butyl (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate as starting material. LCMS calculated for C₂₅H₃₃N₁₀O (M+H)⁺: *m/z* = 489.3; found: 489.1. The product was isolated as the TFA salt.

Example 22. Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate



Step 1. Methyl (3R,5S)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate



5

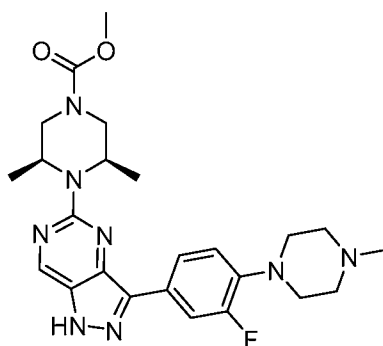
A solution of 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (1.368 g, 3.33 mmol, see Example 1, Step 1), methyl (3R,5S)-3,5-dimethylpiperazine-1-carboxylate (1.721 g, 9.99 mmol), and *N,N*-diisopropylethylamine (3.49 mL, 19.98 mmol) in 1-methyl-2-pyrrolidinone (20 mL) was heated to 120 °C. After 5 days, the reaction mixture was cooled to r.t., quenched with water and EtOAc. The organic layer was washed with brine, dried with MgSO₄ and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₁₉H₃₂IN₆O₃Si (M+H)⁺: m/z = 547.1; found 547.1.

Step 2. Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate

A solution of methyl (3R,5S)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (400 mg, 0.732 mmol), (4-(4-methylpiperazin-1-yl)phenyl)boronic acid (483 mg, 2.196 mmol), XPhos Pd G2 (86 mg, 0.110 mmol), and potassium phosphate (621 mg, 2.93 mmol) in dioxane (10 mL) and water (1 mL) was heated to 70 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 5 mL MeOH and 4 mL HCl (4M in

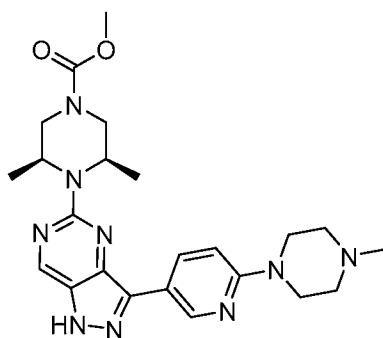
dioxane) and stirred at 60 °C for 1 hr. The resulting mixture was purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS calculated for C₂₄H₃₃N₈O₂ (M+H)⁺: m/z = 465.3; found 465.4. ¹H NMR (500 MHz, DMSO) δ 9.77 (s, 1H), 9.05 (s, 1H), 8.31 (m, 2H), 7.15 (m, 2H), 4.85 (m, 2H), 3.96 (m, 4H), 3.68 (s, 3H), 3.55 (d, *J* = 12.2 Hz, 2H), 3.18 (m, 4H), 3.04 (m, 2H), 2.89 (m, 3H), 1.23 (s, 3H), 1.21 (s, 3H) ppm. The product was isolated as the TFA salt.

Example 23. Methyl (3*R*,5*S*)-4-(3-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate

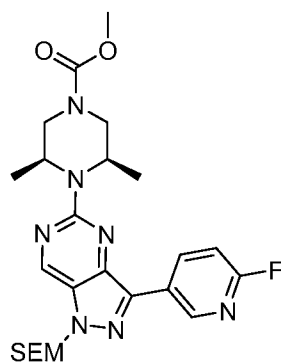


This compound was prepared according to the procedures described in Example 22, using 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-methylpiperazine instead of (4-(4-methylpiperazin-1-yl)phenyl)boronic acid as starting material. LCMS calculated for C₂₄H₃₂FN₈O₂ (M+H)⁺: m/z = 483.3; found: 483.5. The product was isolated as the TFA salt.

Example 24. Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate



*Step 1. Methyl (3*R*,5*S*)-4-(3-(6-fluoropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate*

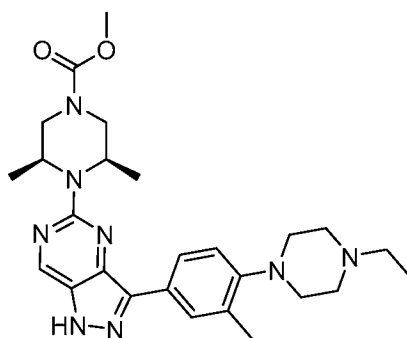


A solution of methyl (3*R*,5*S*)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (100 mg, 0.183 mmol, see Example 22, *Step 1*), (6-fluoropyridin-3-yl)boronic acid (77 mg, 0.549 mmol), Xphos Pd G2 (21.60 mg, 0.027 mmol), and potassium phosphate (136 mg, 0.640 mmol) in dioxane (1.6 mL) and water (0.16 mL) was heated to 75 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was used directly in the next step. LCMS calculated for C₂₄H₃₅FN₇O₃Si (M+H)⁺: m/z = 516.3; found 516.3.

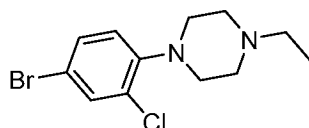
*Step 2. Methyl (3R,5S)-3,5-dimethyl-4-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate*

A solution of methyl (3*R*,5*S*)-4-(3-(6-fluoropyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (20 mg, 0.039 mmol), 1-methylpiperazine (11.65 mg, 0.116 mmol), and *N,N*-diisopropylethylamine (135 µL, 0.776 mmol) in DMSO (1 mL) was heated to 120 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 0.8 mL HCl (4M in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₂₃H₃₂N₉O₂ (M+H)⁺: m/z = 466.3; found: 466.3. The product was isolated as the TFA salt.

Example 25. Methyl (3*R*,5*S*)-4-(3-(4-(4-ethylpiperazin-1-yl)-3-methylphenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate

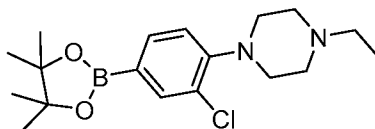


Step 1. 1-(4-Bromo-2-chlorophenyl)-4-ethylpiperazine



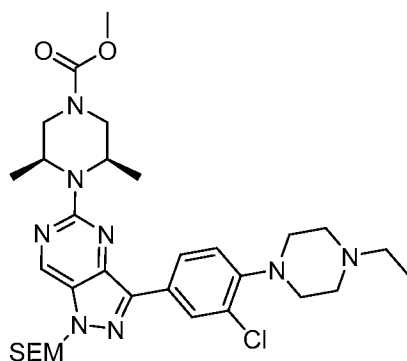
A solution of 1-(4-bromo-2-chlorophenyl)piperazine (100 mg, 0.363 mmol),
 5 acetaldehyde (61 μ L, 1.09 mmol), and sodium triacetoxymethylborate (231 mg, 1.09 mmol) in DCM (5 mL) was stirred at r.t. for 20 hrs. The reaction mixture was then diluted with water and extracted with DCM. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated. The crude was purified by CombiFlash Rf+ Lumen. LCMS calculated for $\text{C}_{12}\text{H}_{17}\text{BrClN}_2$ ($\text{M}+\text{H}$) $^+$: $m/z = 303.0$; found 303.0.

Step 2. 1-(2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-ethylpiperazine



A solution of 1-(4-bromo-2-chlorophenyl)-4-ethylpiperazine (78.6 mg, 0.259 mmol), bis(pinacolato)diboron (65.7 mg, 0.259 mmol), $\text{PdCl}_2\text{dppf} \cdot \text{DCM}$ (31.7 mg, 0.039 mmol), and
 15 potassium acetate (76 mg, 0.777 mmol) in dioxane (2.59 mL) was heated to 85 $^\circ\text{C}$ for 20 hrs. The reaction mixture was cooled to r.t., diluted with EtOAc and filtered through celite. The organic layer was concentrated and purified by CombiFlash Rf+ Lumen. LCMS calculated for $\text{C}_{18}\text{H}_{29}\text{BClN}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$: $m/z = 351.2$; found 351.1.

Step 3. Methyl (3R,5S)-4-(3-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate

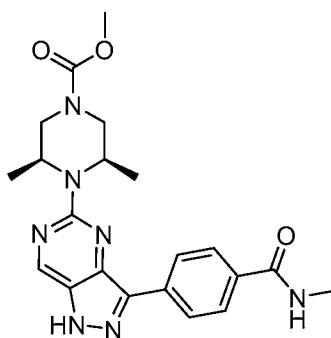


A solution of methyl (3*R*,5*S*)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (49.7 mg, 0.091 mmol, see Example 22, *Step 1*), 1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-ethylpiperazine (32.1 mg, 0.091 mmol), Xphos Pd G2 (14.40 mg, 0.018 mmol), and potassium phosphate (58.3 mg, 0.274 mmol) in dioxane (2 mL) and water (0.2 mL) was heated to 75 °C. After 20 hrs, the reaction mixture was cooled to r.t., diluted with water and EtOAc. The organic layer was concentrated and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₃₁H₄₈ClN₈O₃Si (M+H)⁺: m/z = 643.3; found 643.4.

*Step 4. Methyl (3R,5S)-4-(3-(4-(4-ethylpiperazin-1-yl)-3-methylphenyl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate*

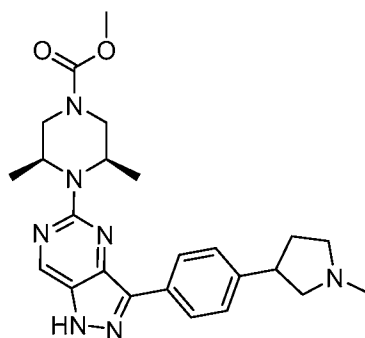
A solution of methyl (3*R*,5*S*)-4-(3-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (30 mg, 0.047 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (65 µL, 0.47 mmol), Xphos Pd G2 (18.35 mg, 0.023 mmol), and potassium phosphate (49.5 mg, 0.233 mmol) in dioxane (2 mL) and water (0.200 mL) was heated to 75 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 0.8 mL HCl (4M in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₂₅H₃₅N₈O₂ (M+H)⁺: m/z = 493.3; found 493.1. The product was isolated as the TFA salt.

Example 26. Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(4-(methylcarbamoyl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate

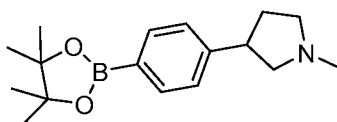


This compound was prepared according to the procedures described in Example 22, using (4-(methylcarbamoyl)phenyl)boronic acid instead of (4-(4-methylpiperazin-1-yl)phenyl)boronic acid as starting material. LCMS calculated for $C_{21}H_{26}N_7O_3$ ($M+H$)⁺: m/z = 424.2; found: 424.1. The product was isolated as the TFA salt.

Example 27. Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(1-methylpyrrolidin-3-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate



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

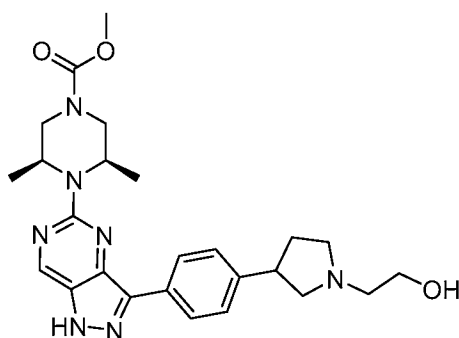


A solution of 3-(4-bromophenyl)-1-methylpyrrolidine (0.23 g, 0.958 mmol), bis(pinacolato)diboron (0.340 g, 1.341 mmol), $PdCl_2dppf$.DCM (0.078 g, 0.096 mmol), and potassium acetate (0.282 g, 2.87 mmol) in dioxane (4.79 mL) was heated to 85 °C for 16 hrs. The reaction mixture was cooled to r.t., diluted with EtOAc and filtered through celite. The organic layer was concentrated and purified by CombiFlash Rf+ Lumen. LCMS calculated for $C_{17}H_{27}BNO_2$ ($M+H$)⁺: m/z = 288.2; found 288.2.

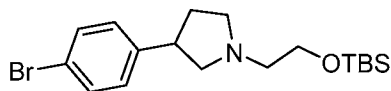
Step 2. Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(1-methylpyrrolidin-3-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate

A solution of methyl (3*R*,5*S*)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (25 mg, 0.046 mmol, see Example 22, *Step 1*), 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (39.4 mg, 0.137 mmol), Xphos Pd G2 (7.2 mg, 9.2 μ mol), and potassium phosphate (34.0 mg, 0.160 mmol) in dioxane (1 mL) and water (0.1 mL) was heated to 75 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 0.8 mL HCl (4M in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₂₄H₃₂N₇O₂ (M+H)⁺: m/z = 450.3; found 450.2. The product was isolated as the TFA salt.

Example 28. Methyl (3*R*,5*S*)-4-(3-(4-(1-(2-hydroxyethyl)pyrrolidin-3-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate



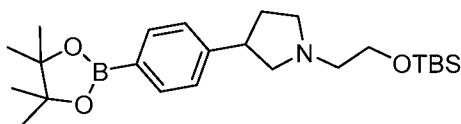
Step 1. 3-(4-Bromophenyl)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)pyrrolidine



A solution of 2-((tert-butyldimethylsilyl)oxy)acetaldehyde (0.239 mL, 1.257 mmol), 3-(4-bromophenyl)pyrrolidine hydrochloride (110 mg, 0.419 mmol), and sodium triacetoxymethylborate (266 mg, 1.257 mmol) in DCM (5 mL) was stirred at r.t. for 20 hrs. The reaction mixture was then diluted with water and extracted with DCM. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was purified by CombiFlash Rf+ Lumen. LCMS calculated for C₁₈H₃₁BrNOSi (M+H)⁺: m/z = 384.1; found 384.1.

Step 2. 1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-

2-yl)phenyl)pyrrolidine

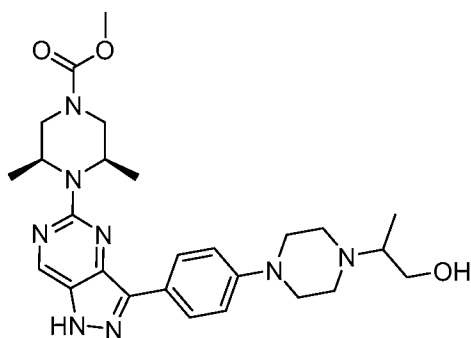


A solution of 3-(4-bromophenyl)-1-(2-((tert-butyl dimethylsilyl)oxy)ethyl)pyrrolidine (205 mg, 0.533 mmol), bis(pinacolato)diboron (190 mg, 0.747 mmol), PdCl₂dppf.DCM (65.3 mg, 0.080 mmol), and potassium acetate (157 mg, 1.600 mmol) in dioxane (4 mL) was heated to 85 °C for 16 hrs. The reaction mixture was cooled to r.t., diluted with EtOAc and filtered through celite. The organic layer was concentrated and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₂₄H₄₃BNO₃Si (M+H)⁺: m/z = 432.3; found 432.2.

Step 3. Methyl (3*R*,5*S*)-4-(3-(4-(1-(2-hydroxyethyl)pyrrolidin-3-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate

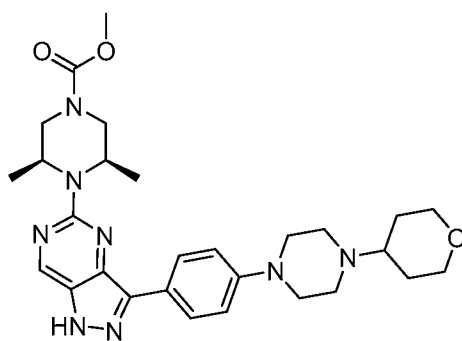
A solution of methyl (3*R*,5*S*)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (30 mg, 0.055 mmol, see Example 22, Step 1), 1-(2-((tert-butyl dimethylsilyl)oxy)ethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (230 mg, 0.533 mmol), Xphos Pd G2 (25.9 mg, 0.033 mmol), and potassium phosphate (69.9 mg, 0.329 mmol) in dioxane (2 mL) and water (0.2 mL) was heated to 75 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 0.8 mL HCl (4M in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₂₅H₃₄N₇O₃ (M+H)⁺: m/z = 480.3; found 480.3. The product was isolated as the TFA salt.

Example 29. Methyl (3*R*,5*S*)-4-(3-(4-(4-(1-hydroxypropan-2-yl)piperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate



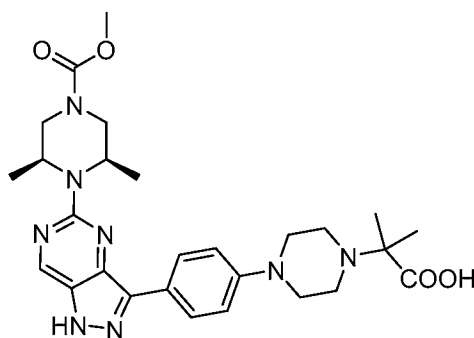
This compound was prepared according to the procedures described in Example 28, using 1-(4-bromophenyl)piperazine and 1-((*tert*-butyldimethylsilyl)oxy)propan-2-one instead of 3-(4-bromophenyl)pyrrolidine hydrochloride and 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde as starting material. LCMS calculated for $C_{26}H_{37}N_8O_3$ ($M+H$)⁺: m/z = 509.3; found: 509.5. The product was isolated as the TFA salt.

Example 30. Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(4-(4-(tetrahydro-2*H*-pyran-4-yl)piperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate

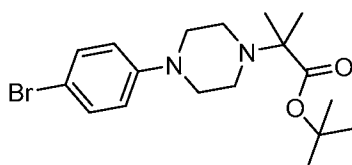


This compound was prepared according to the procedures described in Example 28, using 1-(4-bromophenyl)piperazine and tetrahydro-4*H*-pyran-4-one instead of 3-(4-bromophenyl)pyrrolidine hydrochloride and 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde as starting material. LCMS calculated for $C_{28}H_{39}N_8O_3$ ($M+H$)⁺: m/z = 535.3; found: 535.2. The product was isolated as the TFA salt.

Example 31. 2-(4-(4-(5-((2*R*,6*S*)-4-(Methoxycarbonyl)-2,6-dimethylpiperazin-1-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)phenyl)piperazin-1-yl)-2-methylpropanoic acid

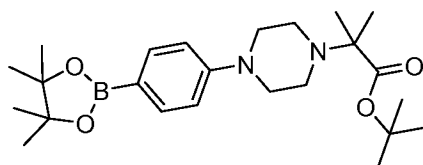


Step 1. *tert*-Butyl 2-(4-(4-bromophenyl)piperazin-1-yl)-2-methylpropanoate



A mixture of 1-(4-bromophenyl)piperazine (138 mg, 0.572 mmol), *tert*-butyl 2-bromo-2-methylpropanoate (0.320 mL, 1.717 mmol), and potassium carbonate (395 mg, 2.86 mmol) in acetonitrile (5 mL) was heated to 85 °C for 3 days. The reaction mixture was then diluted with EtOAc and water. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was purified by CombiFlash Rf+ Lumen. LCMS calculated for C₁₈H₂₈BrN₂O₂ (M+H)⁺: m/z = 383.1; found 383.3.

Step 2. *tert*-Butyl 2-methyl-2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-1-yl)propanoate



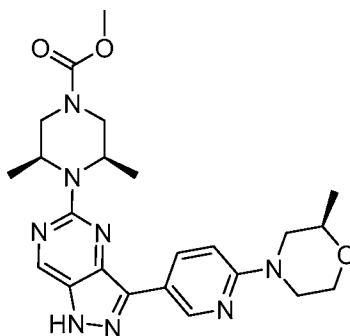
A solution of *tert*-butyl 2-(4-(4-bromophenyl)piperazin-1-yl)-2-methylpropanoate (153 mg, 0.399 mmol), bis(pinacolato)diboron (142 mg, 0.559 mmol), PdCl₂dppf.DCM (48.9 mg, 0.060 mmol), and potassium acetate (118 mg, 1.197 mmol) in dioxane (3 mL) was heated to 85 °C for 20 hrs. The reaction mixture was cooled to r.t., diluted with EtOAc and filtered through celite. The organic layer was concentrated and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₂₄H₄₀BN₂O₄ (M+H)⁺: m/z = 431.3; found 431.5.

Step 3. 2-(4-(4-(5-((2R,6S)-4-(methoxycarbonyl)-2,6-dimethylpiperazin-1-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperazin-1-yl)-2-methylpropanoic acid

A solution of methyl (3R,5S)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-

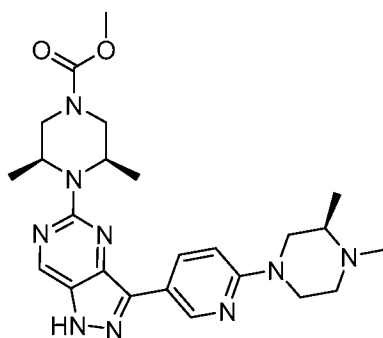
pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (60 mg, 0.110 mmol, see Example 22, *Step 1*), *tert*-butyl 2-methyl-2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-1-yl)propanoate (135 mg, 0.314 mmol), Xphos Pd G2 (12.96 mg, 0.016 mmol), and potassium phosphate (93 mg, 0.439 mmol) in dioxane (1.5 mL) and water (0.150 mL) was heated to 70 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 0.8 mL HCl (4M in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₂₇H₃₇N₈O₄ (M+H)⁺: m/z = 537.3; found 537.4. The product was isolated as the TFA salt.

Example 32. Methyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-2-methylmorpholino)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate



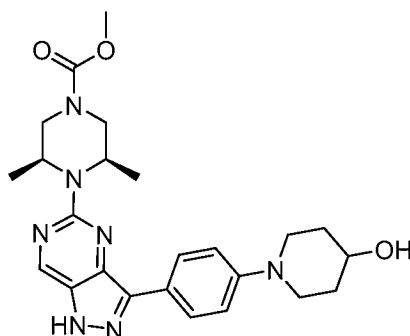
This compound was prepared according to the procedures described in Example 24, using (*R*)-2-methylmorpholine hydrochloride instead of 1-methylpiperazine as starting material. LCMS calculated for C₂₃H₃₁N₈O₃ (M+H)⁺: m/z = 467.2; found: 467.3. The product was isolated as the TFA salt.

Example 33. Methyl (3*R*,5*S*)-4-(3-(6-((*R*)-3,4-dimethylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate

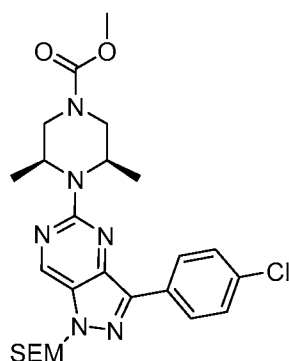


This compound was prepared according to the procedures described in Example 24, using (*R*)-1,2-dimethylpiperazine dihydrochloride instead of 1-methylpiperazine as starting material. LCMS calculated for $C_{24}H_{34}N_9O_2$ ($M+H$)⁺: m/z = 480.3; found: 480.3. The product was isolated as the TFA salt.

Example 34. Methyl (3*R*,5*S*)-4-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate



10 *Step 1. Methyl (3*R*,5*S*)-4-(3-(4-chlorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate*



A solution of methyl (3*R*,5*S*)-4-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (500 mg, 0.915 mmol, see Example 22, *Step 1*), (4-chlorophenyl)boronic acid (0.286 g, 1.830 mmol), $Pd_2(dba)_3$ (0.042 g, 0.046 mmol), tri(*o*-tolyl)phosphine (0.056 g, 0.183 mmol), and potassium

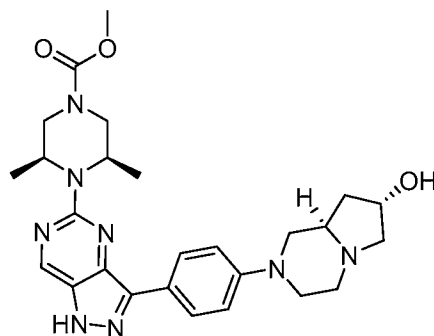
phosphate (0.777 g, 3.66 mmol) in DMF (5 mL) was heated to 80 °C. After 2 days, the reaction mixture was cooled to r.t., diluted with EtOAc and filtered through celite. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The organic layer was concentrated and purified by CombiFlash Rf+ Lumen. LCMS calculated for

5 C₂₅H₃₆ClN₆O₃Si (M+H)⁺: m/z = 531.2; found 531.3.

Step 2. Methyl (3R,5S)-4-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate

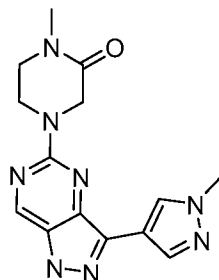
A solution of methyl (3R,5S)-4-(3-(4-chlorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate (12 mg, 0.023 mmol), piperidin-4-ol (4.57 mg, 0.045 mmol), RuPhos Pd G3 (2.83 mg, 3.39 μmol), RuPhos (1.6 mg, 3.4 μmol), and sodium *tert*-butoxide (10.9 mg, 0.113 mmol) in THF (1 mL) was heated to 85 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 0.8 mL HCl (4M in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₂₄H₃₂N₇O₃ (M+H)⁺: m/z = 466.3; found 466.4. The product was isolated as the TFA salt.

Example 35. Methyl (3R,5S)-4-(3-(4-((7S,8aR)-7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate

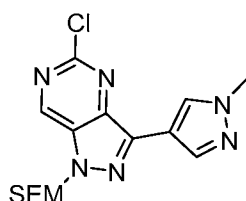


25 This compound was prepared according to the procedures described in Example 34, using (7S,8aR)-octahydropyrrolo[1,2-a]pyrazin-7-ol dihydrochloride instead of piperidin-4-ol as starting material. LCMS calculated for C₂₆H₃₅N₈O₃ (M+H)⁺: m/z = 507.3; found: 507.4. The product was isolated as the TFA salt.

Example 36. 1-Methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one



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



A solution of 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-
 d]pyrimidine (1.0 g, 2.435 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-
 1H-pyrazole (0.507 g, 2.435 mmol), Xphos Pd G2 (0.192 g, 0.243 mmol), and potassium
 10 phosphate (1.550 g, 7.30 mmol) in dioxane (15 mL) and water (1.5 mL) was heated to 75 °C.
 After 20 hrs, the reaction mixture was cooled to r.t., quenched with water and EtOAc. The
 organic layer was washed with brine, dried with Na₂SO₄ and purified by CombiFlash Rf+
 Lumen. LCMS calculated for C₁₅H₂₂ClN₆OSi (M+H)⁺: m/z = 365.1; found 365.1.

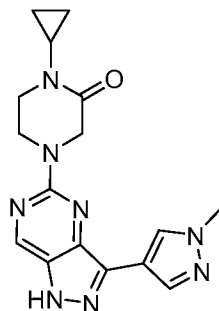
15

Step 2. 1-Methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one

A solution of 5-chloro-3-(1-methyl-1H-pyrazol-4-yl)-1-((2-
 (trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (40 mg, 0.110 mmol), 1-
 20 methylpiperazin-2-one hydrochloride (33.0 mg, 0.219 mmol), and *N,N*-diisopropylethylamine
 (56.7 mg, 0.438 mmol) in dioxane (1 mL) was heated to 100 °C. After 20 hrs, the reaction
 was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was
 washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL
 MeOH and 1 mL HCl (4 M solution in dioxane) and stirred at 60 °C for 2 hrs. The resulting
 25 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). LCMS calculated for

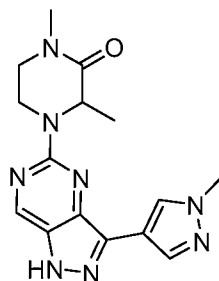
$C_{14}H_{17}N_8O$ ($M+H$)⁺: m/z = 313.1; found 313.1. The product was isolated as the TFA salt.

Example 37. 1-Cyclopropyl-4-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-2-one



This compound was prepared according to the procedures described in Example 36, using 1-cyclopropylpiperazin-2-one instead of 1-methylpiperazin-2-one hydrochloride as starting material. LCMS calculated for $C_{16}H_{19}N_8O$ ($M+H$)⁺: m/z = 339.2; found: 339.0. The product was isolated as the TFA salt.

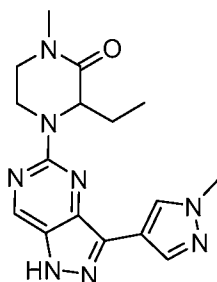
Example 38. 1,3-Dimethyl-4-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-2-one



A solution of 5-chloro-3-(1-methyl-1*H*-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine (40 mg, 0.110 mmol, see Example 36, *Step 1*), 1,3-dimethylpiperazin-2-one hydrochloride (27.1 mg, 0.164 mmol), RuPhos (10.2 mg, 0.022 mmol), RuPhos Pd G3 (18.3 mg, 0.022 mmol), and sodium *tert*-butoxide (31.6 mg, 0.329 mmol) in THF (1 mL) was heated to 85 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated. The crude was taken up in 1 mL MeOH and 1 mL HCl (4 M solution in dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for

$C_{15}H_{19}N_8O$ (M+H)⁺: m/z = 327.2; found 327.1. The product was isolated as the TFA salt.

Example 39. 3-Ethyl-1-methyl-4-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-2-one

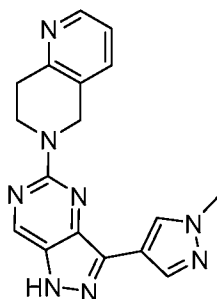


5

This compound was prepared according to the procedures described in Example 38, using 3-ethyl-1-methylpiperazin-2-one instead of 1,3-dimethylpiperazin-2-one hydrochloride as starting material. LCMS calculated for $C_{16}H_{21}N_8O$ (M+H)⁺: m/z = 341.2; found: 341.2. The product was isolated as the TFA salt.

10

Example 40. 6-(3-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine

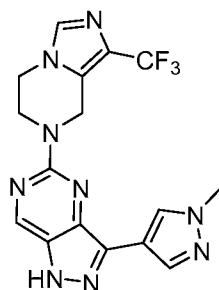


This compound was prepared according to the procedures described in Example 38, using 5,6,7,8-tetrahydro-1,6-naphthyridine instead of 1,3-dimethylpiperazin-2-one hydrochloride as starting material. LCMS calculated for $C_{17}H_{17}N_8$ (M+H)⁺: m/z = 333.2; found: 333.2. The product was isolated as the TFA salt.

15

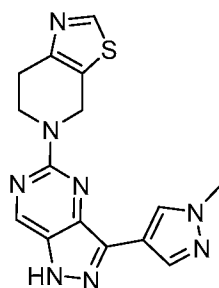
Example 41. 3-(1-Methyl-1*H*-pyrazol-4-yl)-5-(1-(trifluoromethyl)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine

20



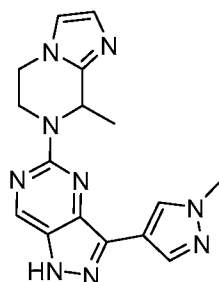
This compound was prepared according to the procedures described in Example 38, using 1-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine instead of 1,3-dimethylpiperazin-2-one hydrochloride as starting material. LCMS calculated for C₁₆H₁₅F₃N₉ (M+H)⁺: m/z = 390.1; found: 390.0. The product was isolated as the TFA salt.

Example 42. 5-(3-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine



This compound was prepared according to the procedures described in Example 38, using 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride instead of 1,3-dimethylpiperazin-2-one hydrochloride as starting material. LCMS calculated for C₁₅H₁₅N₈S (M+H)⁺: m/z = 339.1; found: 339.1. The product was isolated as the TFA salt.

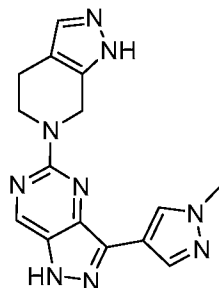
Example 43. 3-(1-Methyl-1H-pyrazol-4-yl)-5-(8-methyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-1H-pyrazolo[4,3-d]pyrimidine



This compound was prepared according to the procedures described in Example 38, using 8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine instead of 1,3-dimethylpiperazin-2-

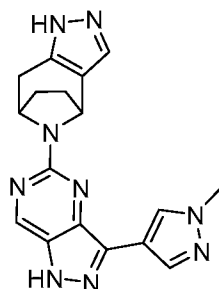
one hydrochloride as starting material. LCMS calculated for $C_{16}H_{18}N_9$ ($M+H$)⁺: m/z = 336.2; found: 336.0. The product was isolated as the TFA salt.

**Example 44. 3-(1-Methyl-1*H*-pyrazol-4-yl)-5-(1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-
5 *c*]pyridin-6-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine**



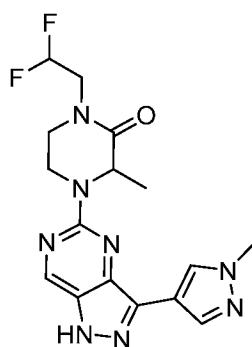
This compound was prepared according to the procedures described in Example 36, using 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine instead of 1-methylpiperazin-2-one hydrochloride as starting material. LCMS calculated for $C_{15}H_{16}N_9$ ($M+H$)⁺: m/z = 322.2; found: 322.2. The product was isolated as the TFA salt.

**Example 45. 9-(3-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-
1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole**

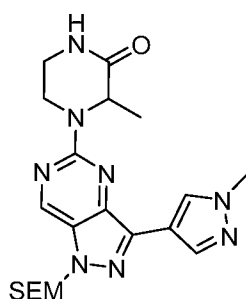


This compound was prepared according to the procedures described in Example 36, using 1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole dihydrochloride instead of 1-methylpiperazin-2-one hydrochloride as starting material. LCMS calculated for $C_{17}H_{18}N_9$ ($M+H$)⁺: m/z = 348.2; found: 348.2. The product was isolated as the TFA salt.

**Example 46. 1-(2,2-Difluoroethyl)-3-methyl-4-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-
20 pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-2-one**



Step 1. 3-Methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one



5 A solution of 5-chloro-3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (610 mg, 1.672 mmol, see Example 36, *Step 1*), 3-methylpiperazin-2-one (620 mg, 5.43 mmol), and *N,N*-diisopropylethylamine (1460 μ L, 8.36 mmol) in DMF (7 mL) was heated at 120 $^{\circ}$ C. After 2 days, the reaction mixture was cooled to r.t., quenched with water and EtOAc. The organic
10 layer was washed with brine, dried with Na₂SO₄ and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₂₀H₃₁N₈O₂Si (M+H)⁺: m/z = 443.2; found 443.5.

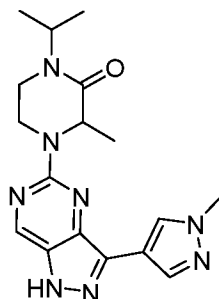
Step 2. 1-(2,2-Difluoroethyl)-3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one

15 A solution of 3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one (25 mg, 0.056 mmol) in THF (1 mL) was added to a vial containing sodium hydride (2.71 mg, 0.068 mmol, 60%). The suspension was added DMF (1 mL) and the resulting solution was stirred at r.t. After 1 hr, 2-bromo-1,1-difluoroethane (13.5 μ L, 0.169 mmol) was added and the solution
20 was stirred at 60 $^{\circ}$ C. After 2 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 1 mL HCl (4 M solution in

dioxane) and stirred at 60 °C for 2 hrs. The resulting 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). LCMS calculated for C₁₆H₁₉F₂N₈O (M+H)⁺: m/z = 377.2; found 377.0. The product was isolated as the TFA salt.

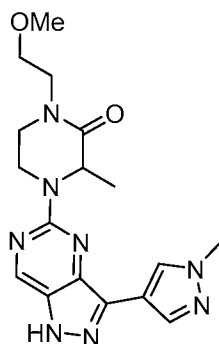
5

Example 47. 1-Isopropyl-3-methyl-4-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-2-one



This compound was prepared according to the procedures described in Example 46, using 2-bromopropane instead of 2-bromo-1,1-difluoroethane as starting material. LCMS calculated for C₁₇H₂₃N₈O (M+H)⁺: m/z = 355.2; found: 355.1. The product was isolated as the TFA salt.

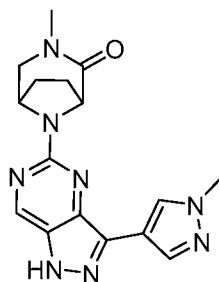
Example 48. 1-(2-Methoxyethyl)-3-methyl-4-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-2-one



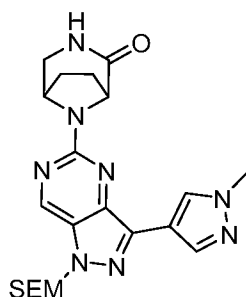
This compound was prepared according to the procedures described in Example 46, using 1-bromo-2-methoxyethane instead of 2-bromo-1,1-difluoroethane as starting material. LCMS calculated for C₁₇H₂₃N₈O₂ (M+H)⁺: m/z = 371.2; found: 371.1. The product was isolated as the TFA salt.

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Example 49. 3-Methyl-8-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-

yl)-3,8-diazabicyclo[3.2.1]octan-2-one

Step 1. 8-(3-(1-Methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



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A solution of 5-chloro-3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (200 mg, 0.548 mmol, see Example 36, *Step 1*), 3,8-diazabicyclo[3.2.1]octan-2-one (138 mg, 1.096 mmol), and *N,N*-diisopropylethylamine (383 μ L, 2.192 mmol) in DMF (3 mL) was heated to 120 $^{\circ}$ C. After 2 days, the reaction mixture was cooled to r.t., quenched with water and EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₂₁H₃₁N₈O₂Si (M+H)⁺: m/z = 455.2; found 455.4.

10

Step 2. 3-Methyl-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one

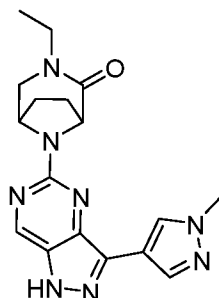
15

A solution of 8-(3-(1-methyl-1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one (45 mg, 0.099 mmol) in THF (1 mL) was added to a vial containing sodium hydride (4.75 mg, 0.119 mmol, 60%). The suspension was added DMF (1 mL) and the resulting solution was stirred at r.t. After 1 hr, iodomethane (148 μ L, 0.297 mmol) was added and the solution was stirred at rt. After 2 hrs, the reaction was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL MeOH and 1 mL HCl (4 M solution in dioxane) and stirred at 60 $^{\circ}$ C for 2 hrs. The resulting mixture was purified with prep-LCMS (XBridge C18 column, eluting with a gradient of

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acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS calculated for $C_{16}H_{19}N_8O$ ($M+H$)⁺: m/z = 339.2; found 339.2. The product was isolated as the TFA salt.

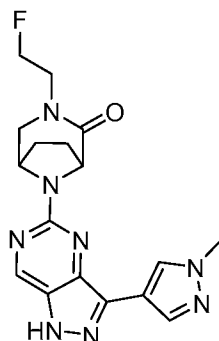
Example 50. 3-Ethyl-8-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



This compound was prepared according to the procedures described in Example 49, using iodoethane instead of iodomethane as starting material. LCMS calculated for $C_{17}H_{21}N_8O$ ($M+H$)⁺: m/z = 353.2; found: 353.1. The product was isolated as the TFA salt.

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Example 51. 3-(2-Fluoroethyl)-8-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one

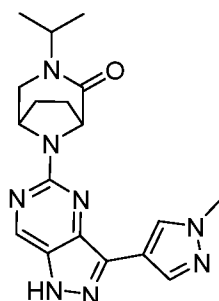


This compound was prepared according to the procedures described in Example 49, using 1-bromo-2-fluoroethane instead of iodomethane as starting material. LCMS calculated for $C_{17}H_{20}FN_8O$ ($M+H$)⁺: m/z = 371.4; found: 371.1. The product was isolated as the TFA salt.

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Example 52. 3-Isopropyl-8-(3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one

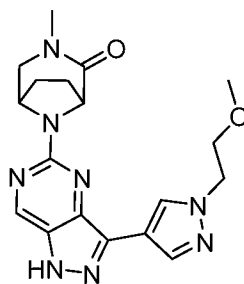
20



This compound was prepared according to the procedures described in Example 49, using 2-bromopropane instead of iodomethane as starting material. LCMS calculated for $C_{18}H_{23}N_8O$ ($M+H$)⁺: m/z = 367.2; found: 367.1. The product was isolated as the TFA salt.

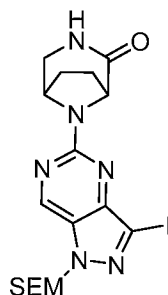
5

Example 53. 8-(3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one



Step 1. 8-(3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one

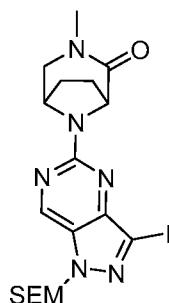
10



A solution of 3,8-diazabicyclo[3.2.1]octan-2-one (98 mg, 0.779 mmol), 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidine (160 mg, 0.390 mmol, see Example 1, *Step 1*), and *N,N*-diisopropylethylamine (272 μ L, 1.558 mmol) in DMSO (2 mL) was heated to 120 °C. After 20 hrs, the reaction mixture was cooled to r.t., quenched with water and EtOAc. The organic layer was washed with brine, dried with Na_2SO_4 and purified by CombiFlash Rf+ Lumen. LCMS calculated for $C_{17}H_{26}IN_6O_2Si$ ($M+H$)⁺: m/z = 501.1; found 501.0.

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Step 2. 8-(3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one

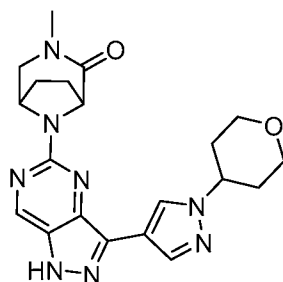


A solution of 8-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-
 5 *d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one (500 mg, 0.999 mmol) in THF (3 mL)
 was added to a vial containing sodium hydride (48.0 mg, 1.199 mmol, 60%). The suspension
 was added DMF (3 mL) and the resulting solution was stirred at r.t. After 1 hr, iodomethane
 (187 μ L, 3.00 mmol) was added and the resulting solution was stirred at r.t. After 2 hrs, the
 reaction was diluted with water and extracted with EtOAc. The organic layer was washed
 10 with brine, dried with Na₂SO₄ and purified by CombiFlash Rf+ Lumen. LCMS calculated for
 C₁₈H₂₈IN₆O₂Si (M+H)⁺: *m/z* = 515.1; found 515.0.

Step 3. 8-(3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one

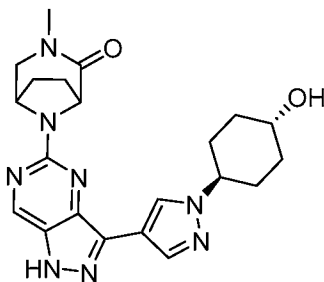
A solution of 8-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-
 15 *d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one (30 mg, 0.058 mmol), 1-(2-
 methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (44.1 mg, 0.175
 mmol), Xphos Pd G2 (4.6 mg, 5.8 μ mol), and potassium phosphate (49.5 mg, 0.233 mmol) in
 dioxane (1 mL) and water (0.1 mL) was heated to 80 °C. After 20 hrs, the reaction was
 20 cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed
 with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL DCM and 1
 mL TFA and stirred at r.t. for 2 hrs. The solvent was then removed *in vacuo*. The crude was
 then taken up in 1 mL MeOH and 0.7 mL NH₄OH (aq) was added. The resulting mixture was
 stirred at r.t. for 5 min and purified with prep-LCMS (XBridge C18 column, eluting with a
 25 gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS
 calculated for C₁₈H₂₃N₈O₂ (M+H)⁺: *m/z* = 383.2; found 383.2. The product was isolated as
 the TFA salt.

Example 54. 3-Methyl-8-(3-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



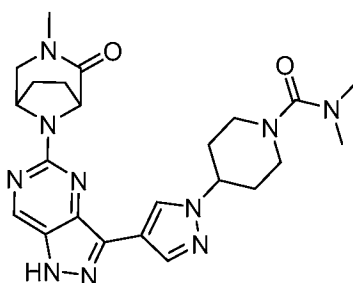
This compound was prepared according to the procedures described in Example 53, using 1-(tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as starting material. LCMS calculated for $C_{20}H_{25}N_8O_2$ ($M+H$)⁺: m/z = 409.2; found: 409.2. The product was isolated as the TFA salt.

Example 55. 8-(3-(1-((1*r*,4*S*)-4-Hydroxycyclohexyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one



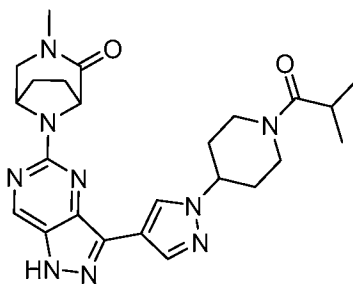
This compound was prepared according to the procedures described in Example 53, using 1-((1*r*,4*r*)-4-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as starting material. LCMS calculated for $C_{21}H_{27}N_8O_2$ ($M+H$)⁺: m/z = 423.2; found: 423.2. The product was isolated as the TFA salt.

Example 56. *N,N*-Dimethyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxamide



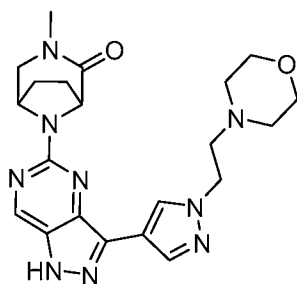
This compound was prepared according to the procedures described in Example 53, using *N,N*-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxamide instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as starting material. LCMS calculated for C₂₃H₃₁N₁₀O₂ (M+H)⁺: m/z = 479.3; found: 479.4. The product was isolated as the TFA salt.

Example 57. 8-(3-(1-(1-Isobutyrylpiperidin-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one



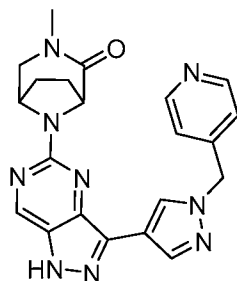
This compound was prepared according to the procedures described in Example 53, using 2-methyl-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidin-1-yl)propan-1-one instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as starting material. LCMS calculated for C₂₄H₃₂N₉O₂ (M+H)⁺: m/z = 478.3; found: 478.1. The product was isolated as the TFA salt.

Example 58. 3-Methyl-8-(3-(1-(2-morpholinoethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



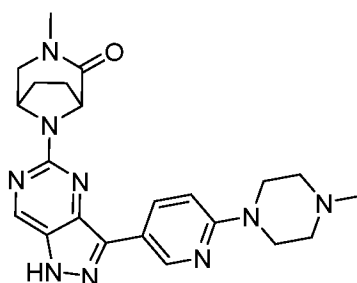
This compound was prepared according to the procedures described in Example 53, using 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethyl)morpholine instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as starting material. LCMS calculated for C₂₁H₂₈N₉O₂ (M+H)⁺: m/z = 438.2; found: 438.4. The product was isolated as the TFA salt.

Example 59. 3-Methyl-8-(3-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



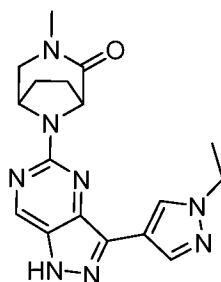
This compound was prepared according to the procedures described in Example 53, using 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl)pyridine instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as starting material. LCMS calculated for C₂₁H₂₂N₉O (M+H)⁺: m/z = 416.2; found: 416.3. The product was isolated as the TFA salt.

Example 60. 3-Methyl-8-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



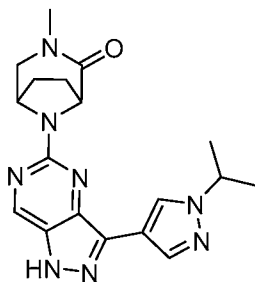
This compound was prepared according to the procedures described in Example 53, using 1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as starting material. LCMS calculated for C₂₂H₂₈N₉O (M+H)⁺: m/z = 434.2; found: 434.2. The product was isolated as the TFA salt.

Example 61. 8-(3-(1-Ethyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one



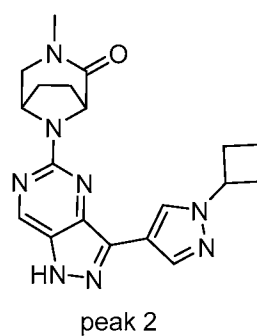
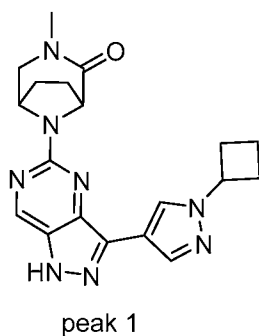
This compound was prepared according to the procedures described in Example 53, using 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as starting material. LCMS calculated for C₁₇H₂₁N₈O (M+H)⁺: m/z = 353.2; found: 353.2. The product was isolated as the TFA salt.

Example 62. 8-(3-(1-Isopropyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one



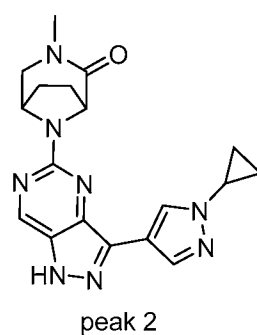
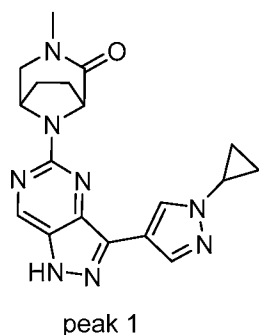
This compound was prepared according to the procedures described in Example 53, using 1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as starting material. LCMS calculated for C₁₈H₂₃N₈O (M+H)⁺: m/z = 367.2; found: 367.3. The product was isolated as the TFA salt.

Example 63 and Example 64. 8-(3-(1-Cyclobutyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one, two enantiomers



The racemic mixture was prepared according to the procedures described in Example 53, using 1-cyclobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as starting material. LCMS calculated for $C_{19}H_{23}N_8O$ ($M+H$)⁺: $m/z = 379.2$; found: 379.2. The product was isolated as the TFA salt. Then, the two enantiomers were separated with chiral SFC (Amylose-1, 2x250 mm, eluting with 40% MeOH in CO₂, at flow rate of 60 mL/min). Example 63: peak 1, $t_R = 3.3$ min. Example 64: peak 2, $t_R = 4.1$ min; ¹H NMR (500 MHz, DMSO) δ 13.29 (s, 1H), 9.05 (s, 1H), 8.42 (s, 1H), 8.14 (s, 1H), 5.01 – 4.90 (m, 2H), 4.78 (d, $J = 6.8$ Hz, 1H), 3.70 – 3.61 (m, 1H), 3.09 (d, $J = 11.7$ Hz, 1H), 2.64 (s, 3H), 2.59 – 2.39 (m, 4H), 2.33 – 2.23 (m, 1H), 2.23 – 2.14 (m, 1H), 2.04 – 1.76 (m, 4H) ppm.

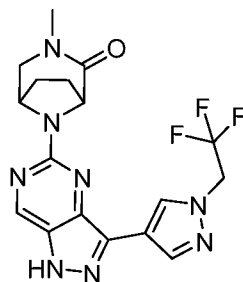
Example 65 and Example 66. 8-(3-(1-Cyclopropyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one, two enantiomers



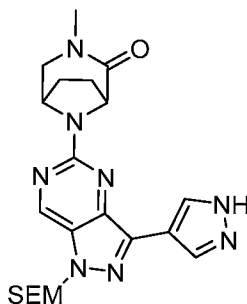
The racemic mixture was prepared according to the procedures described in Example 53, using 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as starting material. LCMS calculated for $C_{18}H_{21}N_8O$ ($M+H$)⁺: $m/z = 365.2$; found: 365.2. The product was isolated as the TFA salt. Then, the two enantiomers were separated with chiral SFC (Amylose-1, 2x250 mm, eluting with 40% MeOH in CO₂, at flow rate of 60 mL/min). Example 65: peak 1, $t_R = 3.1$ min. Example 66: peak 2, $t_R = 3.9$ min; ¹H NMR (500 MHz,

DMSO) δ 13.28 (s, 1H), 9.05 (s, 1H), 8.38 (s, 1H), 8.08 (s, 1H), 4.97 – 4.88 (m, 1H), 4.77 (d, J = 6.8 Hz, 1H), 3.88 – 3.80 (m, 1H), 3.68 – 3.59 (m, 1H), 3.09 (d, J = 11.8 Hz, 1H), 2.64 (s, 3H), 2.33 – 1.84 (m, 4H), 1.16 – 0.96 (m, 4H) ppm.

5 **Example 67. 3-Methyl-8-(3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one**



*Step 1. 8-(3-(1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one*



10

A solution of 8-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one (210 mg, 0.408 mmol, see Example 53, *Step 2*), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (238 mg, 1.225 mmol), XPhos Pd G2 (32.1 mg, 0.041 mmol), and potassium phosphate (347 mg, 1.633 mmol) in dioxane (5 mL) and water (0.5 mL) was heated to 80 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and purified by CombiFlash Rf+ Lumen. LCMS calculated for C₂₁H₃₁N₈O₂Si (M+H)⁺: m/z = 455.2; found 455.4.

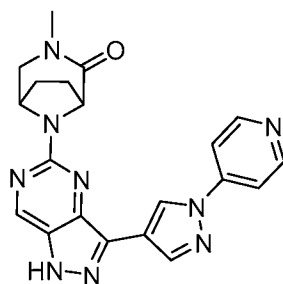
15

20 *Step 2. 3-Methyl-8-(3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one*

A mixture of 8-(3-(1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one (40 mg, 0.088 mmol), 1,1,1-trifluoro-2-iodoethane (17.2 μ L, 0.176 mmol), and Cs₂CO₃ (86 mg, 0.264

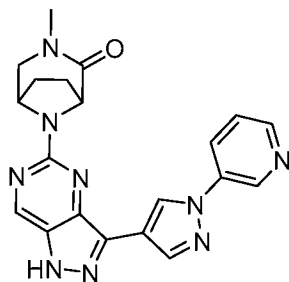
mmol) in DMF (0.880 mL) was heated to 50 °C. After 20 hrs, the reaction was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated. The crude was taken up in 1 mL DCM and 1 mL TFA and stirred at r.t. for 2 hrs. The solvent was then removed *in vacuo*. The crude was then taken up in 1 mL MeOH and 0.7 mL NH₄OH (aq) was added. The resulting mixture was stirred at r.t. for 5 min 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 C₁₇H₁₈F₃N₈O (M+H)⁺: m/z = 407.4; found 407.3. The product was isolated as the TFA salt.

Example 68. 3-Methyl-8-(3-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



This compound was prepared according to the procedures described in Example 53, using 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)pyridine instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as starting material. LCMS calculated for C₂₀H₂₀N₉O (M+H)⁺: m/z = 402.2; found: 402.3. The product was isolated as the TFA salt.

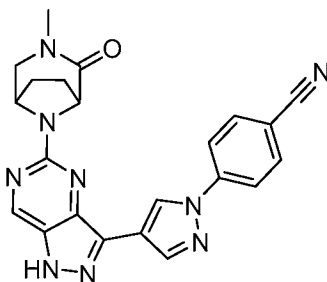
Example 69. 3-Methyl-8-(3-(1-(pyridin-3-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



This compound was prepared according to the procedures described in Example 53, using 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)pyridine instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as starting

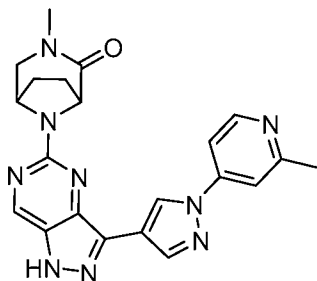
material. LCMS calculated for $C_{20}H_{20}N_9O$ ($M+H$)⁺: $m/z = 402.2$; found: 402.4. The product was isolated as the TFA salt.

Example 70. 4-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile



This compound was prepared according to the procedures described in Example 53, using 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)benzonitrile instead of 1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as starting material. LCMS calculated for $C_{22}H_{20}N_9O$ ($M+H$)⁺: $m/z = 426.2$; found: 426.3. The product was isolated as the TFA salt.

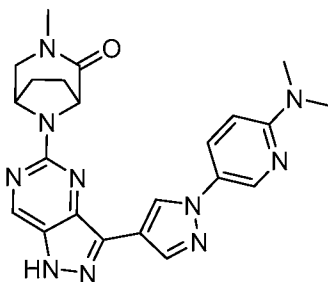
Example 71. 3-Methyl-8-(3-(1-(2-methylpyridin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one



A solution of 8-(3-(1H-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one (40 mg, 0.088 mmol, see Example 67, *Step 1*), (2-methylpyridin-4-yl)boronic acid (36.1 mg, 0.264 mmol), copper (II) acetate (24.0 mg, 0.132 mmol), and pyridine (21.4 μ L, 0.264 mmol) in DCM (1 mL) was stirred at 50 °C. After 20 hrs, the reaction was cooled to r.t., diluted with water and extracted with DCM. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated. The crude was taken up in 1 mL DCM and 1 mL TFA and stirred at r.t. for 2 hrs. The solvent was then removed *in vacuo*. The crude was then taken up in 1 mL MeOH and 0.7 mL NH_4OH (aq) was added. The resulting mixture was stirred at r.t. for 5 min and

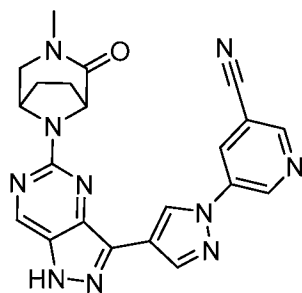
purified with prep-LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% TFA, at flow rate of 60 mL/min). LCMS calculated for $C_{21}H_{22}N_9O$ ($M+H$)⁺: $m/z = 416.2$; found 416.4. The product was isolated as the TFA salt.

5 Example 72. 8-(3-(1-(6-(Dimethylamino)pyridin-3-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one



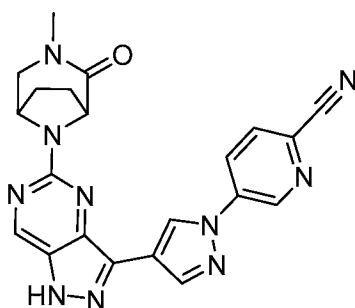
This compound was prepared according to the procedures described in Example 71, using (6-(dimethylamino)pyridin-3-yl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{22}H_{25}N_{10}O$ ($M+H$)⁺: $m/z = 445.2$; found: 445.4. The product was isolated as the TFA salt.

Example 73. 5-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)nicotinonitrile



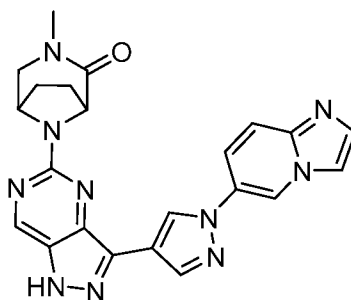
This compound was prepared according to the procedures described in Example 71, using (5-cyanopyridin-3-yl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{21}H_{19}N_{10}O$ ($M+H$)⁺: $m/z = 427.2$; found: 427.4. The product was isolated as the TFA salt.

Example 74. 5-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)picolinonitrile



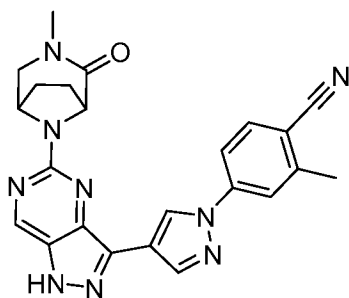
This compound was prepared according to the procedures described in Example 71, using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{21}H_{19}N_{10}O$ (M+H)⁺: m/z = 427.2; found: 427.2. The product was isolated as the TFA salt.

Example 75. 8-(3-(1-(Imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one



This compound was prepared according to the procedures described in Example 71, using imidazo[1,2-a]pyridin-6-ylboronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{22}H_{21}N_{10}O$ (M+H)⁺: m/z = 441.2; found: 441.4. The product was isolated as the TFA salt.

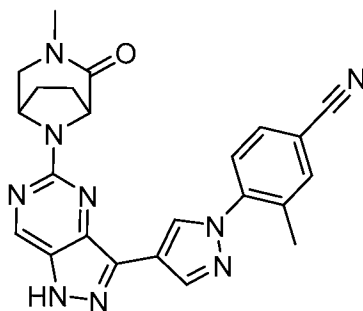
Example 76. 2-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile



This compound was prepared according to the procedures described in Example 71,

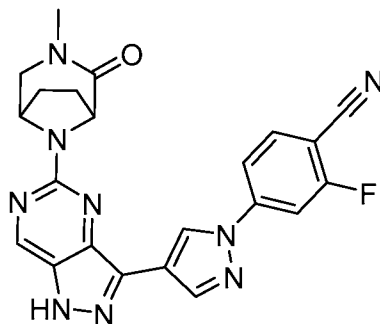
using (4-cyano-3-methylphenyl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{23}H_{22}N_9O$ ($M+H$)⁺: $m/z = 440.2$; found: 440.1. The product was isolated as the TFA salt.

5 **Example 77. 3-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile**



This compound was prepared according to the procedures described in Example 71, using (4-cyano-2-methylphenyl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{23}H_{22}N_9O$ ($M+H$)⁺: $m/z = 440.2$; found: 440.3. The product was isolated as the TFA salt.

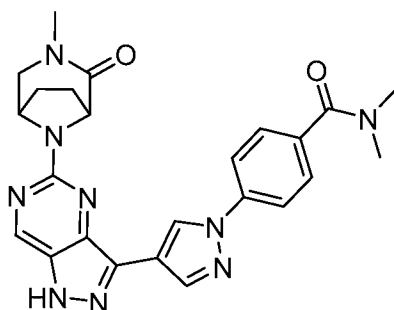
10 **Example 78. 2-Fluoro-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile**



15 This compound was prepared according to the procedures described in Example 71, using (4-cyano-3-fluorophenyl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{22}H_{19}FN_9O$ ($M+H$)⁺: $m/z = 444.2$; found: 444.1. The product was isolated as the TFA salt.

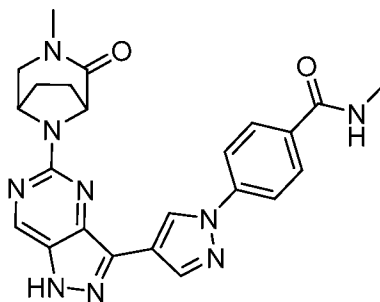
20

Example 79. N,N-Dimethyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide



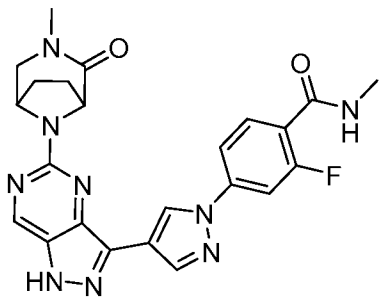
This compound was prepared according to the procedures described in Example 71, using (4-(dimethylcarbamoyl)phenyl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{24}H_{26}N_9O_2$ ($M+H$)⁺: m/z = 472.2; found: 472.4. The product was isolated as the TFA salt.

Example 80. *N*-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide



This compound was prepared according to the procedures described in Example 71, using (4-(methylcarbamoyl)phenyl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{23}H_{24}N_9O_2$ ($M+H$)⁺: m/z = 458.2; found: 458.4. The product was isolated as the TFA salt.

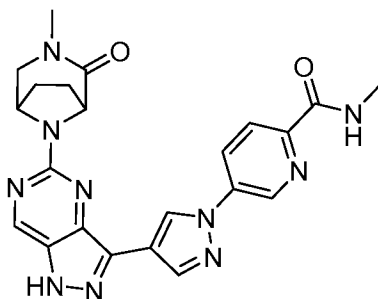
Example 81. 2-Fluoro-*N*-methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-*d*]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide



This compound was prepared according to the procedures described in Example 71,

using (3-fluoro-4-(methylcarbamoyl)phenyl)boronic acid instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{23}H_{23}FN_9O_2$ ($M+H$)⁺: m/z = 476.2; found: 476.2. The product was isolated as the TFA salt.

5 **Example 82. *N*-Methyl-5-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)-1*H*-pyrazol-1-yl)picolinamide**



This compound was prepared according to the procedures described in Example 71, using *N*-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide instead of (2-methylpyridin-4-yl)boronic acid as starting material. LCMS calculated for $C_{22}H_{23}N_{10}O_2$ ($M+H$)⁺: m/z = 459.2; found: 459.2. The product was isolated as the TFA salt.

Example A. ALK2 HTRF Assay

ALK2 (aa 147-end) was obtained from BPS biosciences. The enzymatic assays were conducted in white 384-well polystyrene plates in a final volume of 8 μ L. The inhibitors were serially diluted in DMSO and added to the plate wells prior to addition of the other reaction components. The assays were carried out at 25 $^{\circ}$ C in the assay buffer (50 mM HEPES, pH 7.1, 10% Glycerol, 0.01% Brij50, 10 mM $MgCl_2$, 1 mM EGTA, 5 mM DTT, and 0.01% BSA), containing 50 nM LANCE Ultra ULightTM-DNA Topoisomerase 2-alpha peptide (Perkin Elmer TRF0130), and 3 μ M, 100 μ M or 1 mM ATP (as specified). The final concentration of DMSO in the assay was 1% and the enzyme concentration was 2.5 nM for ALK2. The reactions were allowed to proceed for 2-4 hr after which, the reaction was quenched by addition of EDTA at a final concentration of 20 mM along with 1.5 nM LANCE Ultra Europium-anti-phospho-DNA Topoisomerase 2-alpha (Thr1342) antibody (Perkin Elmer TRF0218). The reaction was read on a PHERAstar FS plate reader (BMG Labtech). IC₅₀ determination was performed by fitting percent control activity versus the log of the inhibitor concentration using the IDBS XLFit and GraphPad Prism 5.0 software.

Compounds of the present disclosure, as exemplified in the Examples, showed IC_{50} values in the following ranges: + = $IC_{50} \leq 100$ nM; ++ = 100 nM < $IC_{50} \leq 500$ nM; +++ = 500 nM < $IC_{50} \leq 2000$ nM; ++++ = $IC_{50} > 2000$ nM. NT = Not tested. Results are shown in Table 1.

5

Example B. ALK2 Cellular Assay

HeLa cells were cultured in MEM media with 10% FBS. Recombinant human BMP-7 was obtained from R&D Systems (cat # 354-BP) and phospho SMAD1 (S463/S465) HTRF kit was purchased from Cisbio (63ADK062PEH). HeLa cells were plated in 96 well flat bottomed plate at 50,000 cells per well and incubated overnight. Next day, media was removed and 50 μ L of fresh complete media was added. 5 μ L compound was added to cells (3 μ M final concentration at highest) and incubated for 60min at 37°C. 200ng/ml BMP-7 was added and incubated for 30min at 37°C. After incubation, the media was removed, washed 2x PBS, and proceeded with HTRF kit according to Cisbio HTRF kit instructions for measuring the Phospho SMAD1 (S463/S465). Finally, both the donor and acceptor were added into 384 well plates and incubated at room temperature overnight and the HTRF signal was measured via Pherastar the next day.

10

Compounds of the present disclosure, as exemplified in the Examples, showed Eu^{3+} Cryptate fluorescent values in the following ranges: * = $PSMAD \leq 100$ nM; ** = 100 nM < $PSMAD \leq 500$ nM; *** = 500 nM < $PSMAD \leq 2000$ nM. NT = Not tested. Results are shown in Table 1.

20

Table 1

Ex #	ALK2 3 μ M IC_{50}	ALK2 100 μ M IC_{50}	ALK2 1mM IC_{50}	ALK2 Cellular Assay PSMAD
1	+	+	+	**
2	+	++	+++	**
3	+	+	++	**
4	+	+	+	**
5	+	++	++	***
6	+	+	+	**
7	+	++	++	**
8	+	+	+	**
9	+	+	+	*
10	+	+	+	*
11	+	+	+	**
12	+	+	+	*
13	+	+	++	**
14	+	+	++	**
15	+	++	+++	***
16	+	NT	++	***

17	+	+	+	*
18	+	+	++	**
19	+	+	++	**
20	+	+	++	**
21	+	+	++	***
22	+	+	+	*
23	+	+	++	**
24	+	+	+	*
25	+	+	NT	**
26	+	NT	++++	NT
27	+	NT	++	**
28	+	+	NT	*
29	+	+	NT	*
30	+	+	NT	**
31	+	+	NT	*
32	+	+	++	**
33	+	+	+	*
34	++	NT	++++	***
35	+	NT	++	**
36	+++	+++	NT	NT
37	NT	NT	NT	NT
38	++	+++	NT	NT
39	NT	NT	NT	NT
40	+++	+++	NT	NT
41	+++	+++	NT	NT
42	NT	NT	NT	NT
43	NT	NT	NT	NT
44	+++	+++	NT	NT
45	+++	+++	NT	NT
46	NT	NT	NT	NT
47	NT	NT	NT	NT
48	NT	NT	NT	NT
49	+++	++++	NT	NT
50	NT	NT	NT	NT
51	++	+++	NT	NT
52	NT	NT	NT	NT
53	NT	NT	NT	NT
54	NT	NT	NT	NT
55	NT	NT	NT	NT
56	NT	NT	NT	NT
57	+++	+++	NT	NT
58	+++	+++	NT	NT
59	+++	+++	NT	NT
60	+	+++	NT	NT
61	+++	+++	NT	NT
62	NT	NT	NT	NT
63	NT	NT	NT	NT
64	++	+++	NT	NT
65	NT	NT	NT	NT
66	NT	NT	NT	NT
67	NT	NT	NT	NT
68	+++	++++	NT	NT
69	NT	NT	NT	NT

70	+++	++++	NT	NT
71	+++	+++	NT	NT
72	+++	+++	NT	NT
73	NT	NT	NT	NT
74	NT	NT	NT	NT
75	+++	+++	NT	NT
76	+++	+++	NT	NT
77	NT	NT	NT	NT
78	NT	NT	NT	NT
79	++	+++	NT	NT
80	NT	NT	NT	NT
81	+++	+++	NT	NT
82	+++	+++	NT	NT

Example C. FGFR Enzymatic Assay

The inhibitor potency of the exemplified compounds was determined in an enzyme discontinuous assay that measures peptide phosphorylation using FRET measurements to
5 detect product formation. Inhibitors were serially diluted in DMSO and a volume of 0.2 μ L was transferred to the wells of a 384-well plate. For the isoforms of FGFR (-1, -2, -3 wild-type and mutant isoforms, -4) including phosphorylated (P) and un-phosphorylated (UP) proteins, a 5 μ L/well volume of enzyme diluted in assay buffer (50 mM HEPES, 10 mM $MgCl_2$, 1 mM EGTA, 0.01% Tween-20, 5 mM DTT, pH 7.5) was added to the plate and pre-
10 incubated with inhibitor for 5 to 15 minutes at ambient temperature. Appropriate controls (enzyme blank and enzyme with no inhibitor) were included on the plate. The reaction was initiated by the addition of a 5 μ L/well volume containing both biotinylated EQEDEPEGDYFEWLE (SEQ ID: 1) peptide substrate and ATP in assay buffer. The 10 μ L/well reaction concentration of the peptide substrate was 500 nM whereas the ATP
15 concentration was maintained near or below the ATP K_m for each FGFR isoform. The ATP K_m values were pre-determined for each FGFR isoform in a separate series of experiments. The reaction plate was incubated at 25 °C for 1 hr and the reactions were ended with the addition of 5 μ L/well of quench solution (50 mM Tris, 150 mM NaCl, 0.5 mg/mL BSA, pH 7.8; 45 mM EDTA, 600 nM staurosporin, with Perkin Elmer Lance Reagents at 3.75 nM Eu-
20 antibody PY20 and 180 nM APC-Streptavidin). The plate was allowed to equilibrate for ~10 minutes at ambient temperature before scanning on a PheraStar plate reader (BMG Labtech) instrument.

Either GraphPad prism or XLfit was used to analyze the data. The IC_{50} values were derived by fitting the data to a four parameter logistic equation producing a sigmoidal dose-

response curve with a variable Hill coefficient. Prism equation: $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{Hill slope}))})$;

XLfit equation: $Y = (A + ((B - A) / (1 + ((X / C)^D))))$ where X is the logarithm of inhibitor concentration and Y is the response.

- 5 Compounds of the present disclosure, as exemplified in the Examples, showed IC_{50} values in the following ranges: + = $\text{IC}_{50} \leq 100 \text{ nM}$; ++ = $100 \text{ nM} < \text{IC}_{50} \leq 500 \text{ nM}$; +++ = $500 \text{ nM} < \text{IC}_{50} \leq 2000 \text{ nM}$; ++++ = $\text{IC}_{50} > 2000 \text{ nM}$. NT = Not tested. Results are shown in Table 2.

10 **Example D. pFGFR2 and pFGFR1,3 Functional Cell HTRF Assay**

To measure phosphorylated Fibroblast Growth Factor Receptor 2 (FGFR2), KATOIII cells (Human Gastric Carcinoma) were purchased from ATCC and maintained in Iscove's with 20% FBS (Gibco/Life Technologies). For the pFGFR2 assay, KATOIII cells were plated overnight in 5% FBS and Iscove's medium at 5×10^4 cells/well into Corning 96-well flat-bottom tissue culture treated plates. The next morning, 50 μl of fresh media with 0.5% FBS
15 was incubated in the presence or absence of a concentration range of test compounds also at 50 μl , for 1 hour at 37°C , 5% CO_2 . Cells were washed with PBS, and lysed with Cell Signaling Lysis Buffer with standard Protease inhibitors for 45 min at room temperature. 4 μl total of Cis Bio Anti Phospho-YAP d2 and Cis Bio Anti Phospho-YAP Cryptate together
20 were added to the lysate and mixed well (following directions of the kit). 16 μl was then transferred to 384 well Greiner white plates and stored at 4°C overnight in the dark. Plates were read on the Pherastar plate reader at 665 nm and 620 nm wavelengths. IC_{50} determination was performed by fitting the curve of inhibitor percent inhibition versus the log of the inhibitor concentration using the GraphPad Prism 5.0 software.

25 To measure phosphorylated Fibroblast Growth Factor Receptor 1 and 3 (FGF1 and FGFR3), in house stable cell lines BAF3-TEL-FGFR1 or BAF3-TEL-FGFR3 were maintained in RPMI with 10% FBS and 1 $\mu\text{g}/\text{ml}$ puromycin (Gibco/Life Technologies). For the assay, 12 nl of BAF3-TEL-FGFR1 or BAF3-TEL-FGFR3 cells in serum free and puromycin free RPMI media at 1×10^6 cell/ml were added to 384 Greiner white plate already
30 containing 20 nl dots of compounds at a concentration range. The plates were gently shaken (100 rpm) for 2 minutes at room temperature to mix well and incubated for 2 hours in a single layer at 37°C , 5% CO_2 . 4 $\mu\text{l}/\text{well}$ of 1/25 dilution of lysis buffer #3 (Cis Bio) was added with standard Protease inhibitors and shaken at 200 rpm at room temperature for 20 minutes. 4 μl total of the Cis Bio Tb-pFGFR Ab (10 ng) and d2-FGFR3 (1 ng) together were added to the

lysate and mixed well. Plates were sealed and incubated at room temperature overnight in the dark. Plates were read on the Pherastar plate reader at 665 nm and 620 nm wavelengths. IC₅₀ determination was performed by fitting the curve of inhibitor percent inhibition versus the log of the inhibitor concentration using the GraphPad Prism 5.0 software.

5 Compounds of the present disclosure, as exemplified in the Examples, showed IC₅₀ values in the following ranges: + = IC₅₀ ≤ 100 nM; ++ = 100 nM < IC₅₀ ≤ 500 nM; +++ = 500 nM < IC₅₀ ≤ 2000 nM; ++++ = IC₅₀ > 2000 nM. NT = Not tested. Results are shown in Table 2.

10 **Example E. Luminescent Viability Assay (LVA, FGFR3)**

RT112 cells were purchased from ATCC (Manassas, VA) and maintained in RPMI, 10% FBS (Gibco/Life Technologies). To measure the effect of test compounds on the viability of cells, the cells were plated with RPMI 10 % FBS (5x10³ cells/well/in 50 µL) into black 96-well Greiner polystyrene in the presence or absence of 50 µl of a concentration
15 range of test compounds. After 3 days, 100 µl of CellTiter-Glo Reagent (Promega) was added. Luminescence was read with a TopCount (PerkinElmer). IC₅₀ determination was performed by fitting the curve of percent inhibition versus the log of the inhibitor concentration using the GraphPad Prism 5.0 software.

Compounds of the present disclosure, as exemplified in the Examples, showed IC₅₀
20 values in the following ranges: + = IC₅₀ ≤ 100 nM; ++ = 100 nM < IC₅₀ ≤ 500 nM; +++ = 500 nM < IC₅₀ ≤ 2000 nM; ++++ = IC₅₀ > 2000 nM. NT = Not tested. Results are shown in Table 2.

Table 2

Ex #	FGFR3 (UP) IC ₅₀ (nM)	FGFR2 (P) IC ₅₀ (nM)	FGFR1 (UP) IC ₅₀ (nM)	FGFR2 (UP) IC ₅₀ (nM)	FGFR1 HTRF IC ₅₀	FGFR2 HTRF IC ₅₀	FGFR3 HTRF IC ₅₀	LVA, FGFR3 IC ₅₀
1	+	+	++	NT	NT	NT	NT	NT
2	+	++	++	NT	NT	NT	NT	NT
3	++	NT	+++	++	NT	NT	NT	NT
4	+	+	++	NT	NT	NT	NT	NT
5	++++	++++	++++	NT	NT	NT	NT	NT
6	+++	NT	++++	+++	NT	NT	NT	NT
7	+++	+++	+++	NT	NT	NT	NT	NT
8	NT	NT	NT	NT	NT	NT	NT	NT
9	++	NT	+++	++	NT	NT	NT	NT
10	+++	NT	+++	+++	NT	NT	NT	NT
11	+++	NT	+++	+++	NT	NT	NT	NT
12	++	NT	+++	++	NT	NT	NT	NT
13	++	NT	+++	++	NT	NT	NT	NT

14	++++	NT	++++	++++	NT	NT	NT	NT
15	++++	++++	++++	NT	NT	NT	NT	NT
16	++	NT	++	++	NT	NT	NT	NT
17	+	NT	++	+	NT	NT	NT	NT
18	++	++	++	NT	NT	NT	NT	NT
19	++	++	+++	NT	NT	NT	NT	NT
20	++++	NT	+++	+++	NT	NT	NT	NT
21	++++	NT	++++	++++	NT	NT	NT	NT
22	++	NT	+++	++	NT	NT	NT	NT
23	++	NT	++	++	NT	NT	NT	NT
24	++	NT	+++	++	NT	NT	NT	NT
25	NT	NT	NT	NT	NT	NT	NT	NT
26	++	NT	+++	++	NT	NT	NT	NT
27	NT	NT	NT	NT	NT	NT	NT	NT
28	++	NT	+++	++	NT	NT	NT	NT
29	+++	NT	++	+++	NT	NT	NT	NT
30	++	NT	+++	++	NT	NT	NT	NT
31	++	NT	+++	++	NT	NT	NT	NT
32	++	NT	++++	+++	NT	NT	NT	NT
33	+	NT	++	++	NT	NT	NT	NT
34	+++	NT	++++	+++	NT	NT	NT	NT
35	NT	NT	NT	NT	NT	NT	NT	NT
36	++	++	+++	NT	NT	NT	NT	NT
37	++	+++	++++	NT	NT	NT	NT	NT
38	+	+	++	NT	NT	NT	NT	++
39	+	+	++	NT	NT	NT	NT	++
40	+	++	+++	NT	NT	NT	NT	+++
41	+	++	++	NT	NT	NT	NT	++
42	+	++	+++	NT	NT	NT	NT	++
43	++	++	+++	NT	NT	NT	NT	NT
44	+	+	++	NT	NT	NT	NT	+++
45	+	+	+	+	+++	NT	++	++
46	+	+	++	NT	NT	NT	NT	++
47	+	++	+++	NT	NT	NT	NT	+++
48	++	+++	++++	NT	NT	NT	NT	NT
49	+	+	+	+	+++	NT	+	++
50	+	+	++	NT	++	NT	++	++
51	+	++	++	NT	NT	NT	NT	+++
52	+	+	++	NT	++NT	NT	++	++
53	+	+	++	NT	NT	NT	NT	+++
54	+	+	++	NT	NT	NT	NT	+++
55	+	+	++	NT	NT	NT	NT	++++
56	+	+	++	NT	NT	NT	NT	+++
57	+	+	++	NT	NT	NT	NT	+++
58	+	+	++	NT	NT	NT	NT	+++
59	+	+	++	NT	NT	NT	NT	+++
60	+	+	+	NT	NT	NT	NT	++
61	+	+	++	NT	NT	NT	+	++
62	+	+	++	NT	NT	NT	++	++
63	++	+++	++++	NT	NT	NT	NT	NT
64	+	+	+	+	NT	+	+	+
65	+++	+++	++++	NT	NT	NT	NT	NT
66	+	+	+	NT	NT	+	+	+

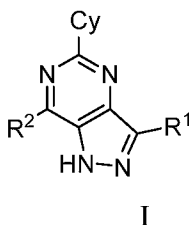
67	+	++	++	NT	NT	NT	++	NT
68	+	+	+	+	NT	+	+	++
69	+	+	+	NT	NT	NT	+	++
70	+	+	+	+	NT	+	+	+
71	+	+	+	NT	NT	+	+	+
72	+	+	+	+	NT	+	+	++
73	+	+	++	NT	NT	NT	NT	+++
74	+	+	+	NT	NT	NT	NT	++
75	+	+	+	NT	NT	NT	NT	+++
76	+	+	+	+	NT	+	+	+
77	+	++	+++	NT	NT	NT	NT	+++
78	+	+	++	NT	NT	NT	NT	++
79	+	+	+	+	NT	NT	+	NT
80	+	+	+	+	NT	NT	NT	+++
81	+	+	+	NT	NT	+	+	+
82	+	+	+	NT	NT	NT	++	NT

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

5 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:

R¹ is selected from Cy¹, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=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 C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each substituted with 1, 2, 3, or 4 substituents independently selected from R¹⁰;

Cy¹ is selected from C₄₋₈ cycloalkyl, 4-12 membered heterocycloalkyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl; wherein the 4-12 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the C₄₋₈ cycloalkyl, 4-12 membered heterocycloalkyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R¹⁰;

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰;

R² is selected from H, D, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy and C₁₋₄ haloalkoxy;

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, D, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $C(=NR^{e1})R^{b1}$, $C(=NOR^{a1})R^{b1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, 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} ;

or two R^{10} substituents taken together with the carbon atom to which they are attached form a spiro 4-7-membered heterocycloalkyl ring, or a spiro C_{3-6} cycloalkyl ring; wherein each spiro 4-7-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 4-7-membered heterocycloalkyl ring is optionally substituted by oxo to form a carbonyl group; and wherein the spiro 4-7-membered heterocycloalkyl ring and spiro C_{3-6} cycloalkyl ring 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, 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, D, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$; 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} ;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkylene, 4-7 membered heterocycloalkyl- C_{1-3} alkylene,

C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, 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}, NR^{c5}C(O)OR^{a5}, NR^{c5}S(O)R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

each R²⁰ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, NO₂, 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}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NOR^{a2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

each R²¹ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, 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}, NR^{c4}C(O)OR^{a4}, NR^{c4}S(O)R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, and S(O)₂NR^{c4}R^{d4}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²²;

each R²² is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃

alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, OR^{a6}, SR^{a6}, C(O)R^{b6}, C(O)NR^{c6}R^{d6}, C(O)OR^{a6}, NR^{c6}R^{d6}, NR^{c6}C(O)R^{b6}, NR^{c6}C(O)OR^{a6}, NR^{c6}S(O)R^{b6}, NR^{c6}S(O)₂R^{b6}, NR^{c6}S(O)₂NR^{c6}R^{d6}, S(O)R^{b6}, S(O)NR^{c6}R^{d6}, S(O)₂R^{b6}, and S(O)₂NR^{c6}R^{d6}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

each R^a, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹⁰;

or any R^c and R^d 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 R¹⁰;

each R^b is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹⁰;

each R^e is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆ alkyl)aminosulfonyl;

each R^{a1}, R^{c1} and R^{d1} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃

alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹¹;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R¹¹;

each R^{b1} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹¹;

each R^{e1} is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆ alkyl)aminosulfonyl;

each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R²¹;

each R^{b2} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²¹;

each R^{e2} is independently selected from H, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylaminosulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆ alkyl)aminosulfonyl;

each R^{a3}, R^{c3} and R^{d3} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹²;

or any R^{c3} and R^{d3} 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 R¹²;

each R^{b3} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R¹²;

each R^{a4}, R^{c4} and R^{d4} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene,

phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²²;

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 R²²;

each R^{b4} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkylene, 4-7 membered heterocycloalkyl-C₁₋₃ alkylene, phenyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²²;

each R^{a5}, R^{c5} and R^{d5} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

or any R^{c5} and R^{d5} 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^g;

each R^{b5} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

each R^{a6}, R^{c6} and R^{d6} is independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g;

or any R^{c6} and R^{d6} 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^g;

each R^{b6} is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO₂, CN, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₂ alkylene, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₁₋₃ alkoxy-C₁₋₃ alkoxy, HO-C₁₋₃ alkoxy, HO-C₁₋₃ alkyl, cyano-C₁₋₃ alkyl, H₂N-C₁₋₃ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, thio, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, carbamyl, C₁₋₆ alkylcarbamyl, di(C₁₋₆ alkyl)carbamyl, carboxy, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆ alkyl)aminosulfonyl, aminosulfonylamino, C₁₋₆ alkylaminosulfonylamino, di(C₁₋₆ alkyl)aminosulfonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, and di(C₁₋₆ alkyl)aminocarbonylamino.

2. The compound of claim 1, wherein R¹ is selected from Cy¹, C₁₋₆ haloalkyl, halo, CN, OR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, NR^cR^d, and NR^cC(O)R^b.

3. The compound of claim 1, wherein R¹ is Cy¹.

4. The compound of any one of claims 1-3, wherein Cy¹ is selected from C₆₋₁₀ 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 5-10 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the C₆₋₁₀ aryl and 5-10 membered heteroaryl are each optionally substituted with 1, 2 or 3 substituents independently selected from R¹⁰.

5. The compound of any one of claims 1-3, wherein Cy¹ is C₆₋₁₀ aryl optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

6. The compound of any one of claims 1-3, wherein Cy¹ is phenyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

7. The compound of any one of claims 1-3, wherein Cy¹ is 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 5-10 membered heteroaryl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

8. The compound of any one of claims 1-3, wherein Cy¹ is 5-6 membered heteroaryl; wherein the 5-6 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 5-6 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the 5-6 membered heteroaryl is optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

9. The compound of any one of claims 1-3, wherein Cy¹ is pyridinyl optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

10. The compound of any one of claims 1-3, wherein Cy¹ is selected from pyrazolyl, phenyl and pyridinyl, wherein the pyrazolyl, phenyl and pyridinyl are each optionally substituted with 1 or 2 substituents independently selected from R¹⁰.

11. The compound of any one of claims 1-10, wherein R¹⁰ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, CN, OR^{a1}, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, and C(O)NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

12. The compound of any one of claims 1-10, wherein R¹⁰ is selected from C₁₋₆ alkyl, halo, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, and C(O)NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene, are each optionally substituted with 1 or 2 substituents independently selected from R¹¹.

13. The compound of any one of claims 1-10, wherein R^{10} is 4-10 membered heterocycloalkyl optionally substituted with 1 or 2 substituents independently selected from R^{11} .
14. The compound of any one of claims 1-10, wherein R^{10} is 5-6 membered heterocycloalkyl optionally substituted with 1 or 2 substituents independently selected from R^{11} .
15. The compound of any one of claims 1-10, wherein R^{10} is piperazinyl optionally substituted with 1 or 2 substituents independently selected from R^{11} .
16. The compound of any one of claims 1-10, wherein R^{10} is selected from methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, fluoro, methylcarbamoyl, phenyl, piperazinyl, pyrrolidinyl, morpholino, piperidinyl, pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, tetrahydropyranyl, cyclohexyl, 2-morpholinoethyl, pyridinylmethyl, 2,2,2-trifluoroethyl, and imidazo[1,2-a]pyridin-6-yl; wherein said methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methylcarbamoyl, phenyl, piperazinyl, pyrrolidinyl, morpholino, piperidinyl, pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, tetrahydropyranyl, cyclohexyl, 2-morpholinoethyl, pyridinylmethyl, 2,2,2-trifluoroethyl, and imidazo[1,2-a]pyridin-6-yl are each optionally substituted with 1 or 2 substituents independently selected from R^{11} .
17. The compound of any one of claims 1-16, wherein R^{11} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3} , $C(O)NR^{c3}R^{d3}$, $C(O)R^{b3}$, and $NR^{c3}R^{d3}$, wherein said C_{1-6} alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R^{12} .
18. The compound of any one of claims 1-16, wherein R^{11} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.
19. The compound of any one of claims 1-16, wherein R^{11} is C_{1-6} alkyl.
20. The compound of any one of claims 1-16, wherein R^{11} is methyl.

21. The compound of any one of claims 1-10, wherein R¹⁰ is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, fluoro, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, methylcarbamoyl, 1-methylpyrrolidin-3-yl, 1-(2-hydroxyethyl)pyrrolidin-3-yl, 4-(1-hydroxypropan-2-yl)piperazin-1-yl, 4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl, 4-(2-carboxypropan-2-yl)piperazin-1-yl, 2-methylmorpholino, 3,4-dimethylpiperazin-1-yl, 4-hydroxypiperidin-1-yl, 7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 2-methoxyethyl, tetrahydro-2H-pyran-4-yl, 4-hydroxycyclohexyl, 1-(dimethylcarbamoyl)piperidin-4-yl, 1-isobutyrylpiperidin-4-yl, 2-morpholinoethyl, 4-methylpiperazin-1-yl, pyridin-4-ylmethyl, 2,2,2-trifluoroethyl, pyridin-4-yl, pyridin-3-yl, 4-cyanophenyl, 2-methylpyridin-4-yl, 6-(dimethylamino)pyridin-3-yl, 5-cyanopyridin-3-yl, 6-cyanopyridin-3-yl, imidazo[1,2-a]pyridin-6-yl, 4-cyano-3-methylphenyl, 4-cyano-2-methylphenyl, 4-cyano-3-fluorophenyl, 4-(methylcarbamoyl)phenyl, 4-(dimethylcarbamoyl)phenyl, 3-fluoro-4-(methylcarbamoyl)phenyl, 3-(6-(methylcarbamoyl)pyridin-3-yl, 3-methylpiperazin-1-yl or 4-methylpiperazin-1-yl.

22. The compound of any one of claims 1-21, wherein R² is H.

23. The compound of any one of claims 1-22, wherein Cy is 4-8 membered heterocycloalkyl; wherein the 4-8 membered heterocycloalkyl 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 4-8 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-8 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-8 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-8 membered heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

24. The compound of any one of claims 1-23, wherein R²⁰ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, and NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹.

25. The compound of any one of claims 1-23, wherein R^{20} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, halo, CN, OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and C_{6-10} aryl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} .

26. The compound of any one of claims 1-23, wherein each R^{20} is C_{1-6} alkyl optionally substituted with 1 or 2 substituents independently selected from R^{21} .

27. The compound of any one of claims 1-23, wherein R^{20} is C_{6-10} aryl optionally substituted with 1 or 2 substituents independently selected from R^{21} .

28. The compound of any one of claims 1-23, wherein R^{20} is selected from OR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, and $C(O)OR^{a2}$.

29. The compound of any one of claims 1-28, wherein R^{21} is selected from halo, CN, and OR^{a4} .

30. The compound of any one of claims 1-29, wherein 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, 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 or 2 substituents independently selected from R^{21} .

31. The compound of any one of claims 1-30, wherein each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} .

32. The compound of any one of claims 1-30, wherein any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R^{21} .

33. The compound of any one of claims 1-32, wherein R^{b2} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-}

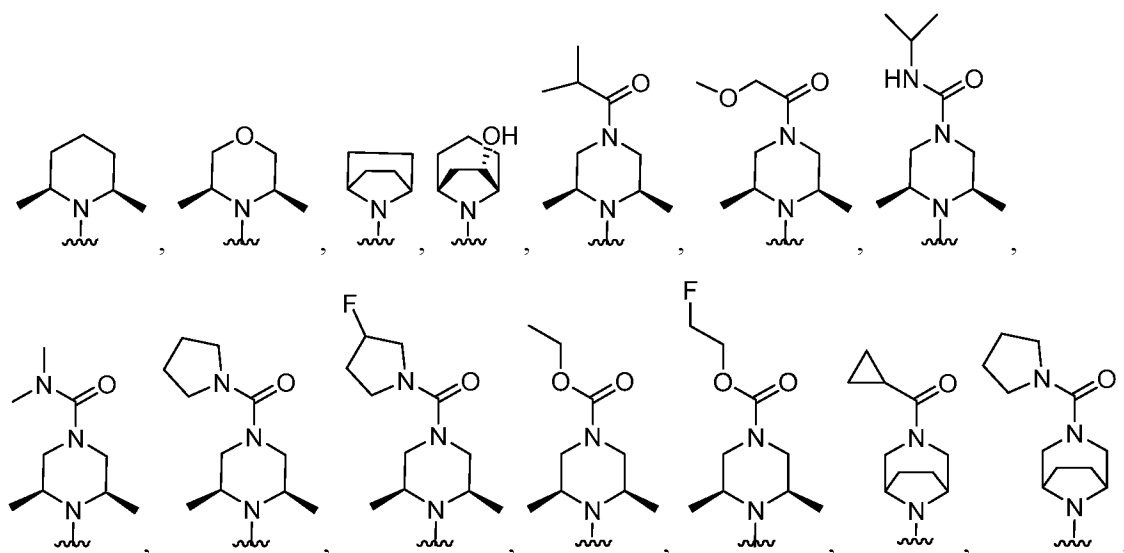
10 cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R²¹.

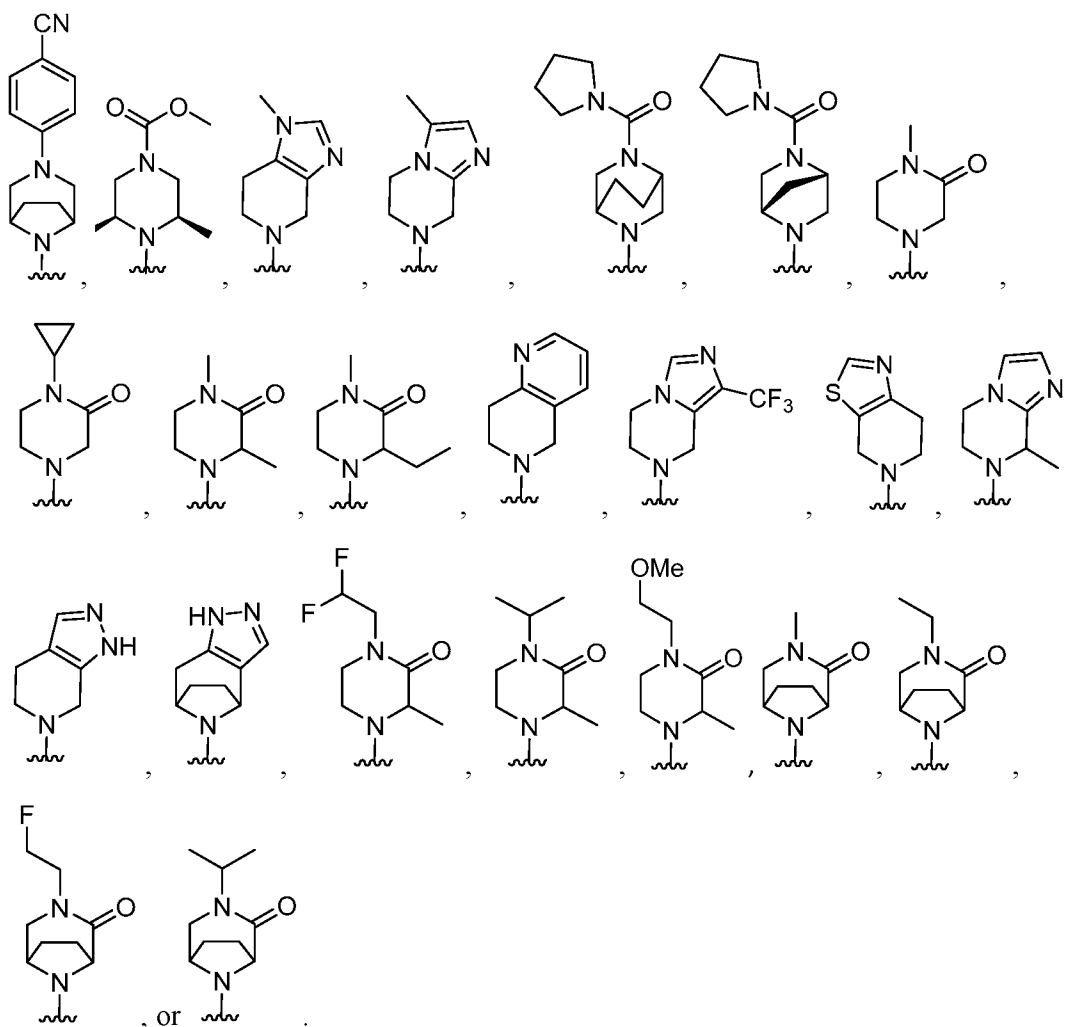
34. The compound of any one of claims 1-33, wherein each R^{a4}, R^{c4} and R^{d4} is independently selected from H and C₁₋₆ alkyl.

35. The compound of any one of claims 1-33, wherein each R^{a4}, R^{c4} and R^{d4} is independently C₁₋₆ alkyl.

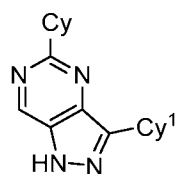
36. The compound of any one of claims 1-22, wherein Cy is piperidinyl, morpholinyl, azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, piperazinyl, diazabicyclo[3.2.1]octanyl, 1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl, 5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 3-oxopiperazinyl, 5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-7-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-5-yl, 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl, 1,4,5,6,7,8-hexahydro-5,8-epiminocyclohepta[c]pyrazol-9-yl, or 2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl, each optionally substituted with 1, 2, 3, or 4 substituents independently selected from R²⁰.

37. The compound of any one of claims 1-22, wherein Cy is





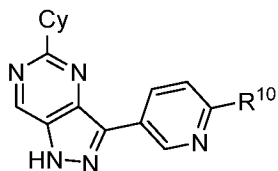
38. The compound of claim 1, wherein the compound is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof.

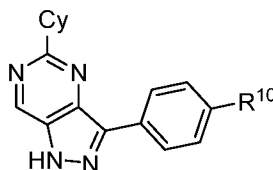
39. The compound of claim 1, wherein the compound is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof.

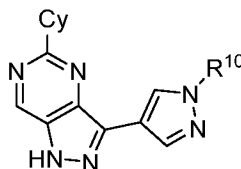
40. The compound of claim 1, wherein the compound is a compound of Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

41. The compound of claim 1, wherein the compound is a compound of Formula V:



V

or a pharmaceutically acceptable salt thereof.

42. The compound of claim 1, wherein:

R^1 is Cy^1 ;

Cy^1 is selected from C_{5-6} cycloalkyl, 5-6 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl; wherein the 5-6 membered heterocycloalkyl and 5-6 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 5-6 membered heteroaryl and 5-6 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; and wherein the C_{5-6} cycloalkyl, 5-6 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl are each optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{10} ;

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally

substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R²⁰;

R² is selected from H, D, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

each R¹⁰ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene, 5-10 membered heteroaryl-C₁₋₃ alkylene, halo, D, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, and NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl-C₁₋₃ alkylene, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, C₆₋₁₀ aryl-C₁₋₃ alkylene and 5-10 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3}, C(O)NR^{c3}R^{d3}, C(O)R^{b3}, and NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹²;

each R¹² is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, and C(O)OR^{a5};

each R²⁰ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, CN, NO₂, 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}, and NR^{c2}C(O)OR^{a2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R²¹ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, halo, D, CN, and OR^{a4};

each R^{a1}, R^{c1} and R^{d1} is independently selected from H, and C₁₋₆ alkyl;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{11} ;

each R^{b1} is independently selected from C_{1-6} alkyl;

each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

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 4-10 membered heterocycloalkyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{a3} , R^{c3} and R^{d3} is independently selected from H, C_{1-6} alkyl, 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_{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} ;

or any R^{c3} and R^{d3} 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^{12} ;

each R^{b3} is independently selected from C_{1-6} alkyl, 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_{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} is independently selected from H, and C_{1-6} alkyl; and

each R^{a5} is independently selected from H, and C_{1-6} alkyl.

43. The compound of claim 1, wherein:

R^1 is Cy^1 ;

Cy^1 is selected from phenyl and 5-6 membered heteroaryl; wherein the 5-6 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 5-6 membered heteroaryl is optionally substituted by oxo to form a carbonyl group; and wherein the phenyl and 5-6 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹⁰;

Cy is 4-14 membered heterocycloalkyl; wherein the 4-14 membered heterocycloalkyl 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 4-14 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-14 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-14 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-14 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R²⁰;

R² is H or D;

each R¹⁰ is independently selected from C₁₋₆ alkyl, halo, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, 5-6 membered heteroaryl-C₁₋₃ alkylene, and C(O)NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3}, C(O)NR^{c3}R^{d3}, C(O)R^{b3}, and NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹²;

each R^{c1} and R^{d1} is independently selected from H, and C₁₋₆ alkyl;

each R^{a3}, R^{b3}, R^{c3} and R^{d3} is independently selected from H, and C₁₋₆ alkyl;

each R¹² is independently selected from C₁₋₆ alkyl, C(O)OH, and OH;

each R²⁰ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, halo, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, and C(O)OR^{a2}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and C₆₋₁₀ aryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{a2} , R^{c2} and R^{d2} is independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl; wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

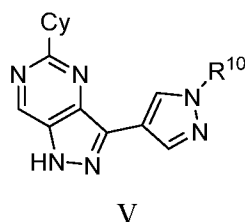
or any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{b2} is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{21} ;

each R^{21} is independently selected from halo, D, CN, and OR^{a4} ; and

each R^{a4} is C_{1-6} alkyl.

44. The compound of claim 1, wherein the compound is a compound of Formula V:



or a pharmaceutically acceptable salt thereof, wherein:

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R^{20} ;

R^{10} is selected from C_{1-6} alkyl, halo, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl- C_{1-3} alkylene, 5-6 membered heteroaryl- C_{1-3} alkylene, and $C(O)NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10

membered heterocycloalkyl-C₁₋₃ alkylene, and 5-6 membered heteroaryl-C₁₋₃ alkylene are each optionally substituted with 1 or 2 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, CN, OR^{a3}, C(O)NR^{c3}R^{d3}, C(O)R^{b3}, and NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, 4-10 membered heterocycloalkyl, and 5-10 membered heteroaryl are each optionally substituted with 1 or 2 substituents independently selected from R¹²;

each R^{c1} and R^{d1} is independently selected from H, and C₁₋₆ alkyl;

each R^{a3}, R^{b3}, R^{c3} and R^{d3} is independently selected from H, and C₁₋₆ alkyl;

each R¹² is independently selected from C₁₋₆ alkyl, C(O)OH, and OH;

each R²⁰ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, halo, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, and C(O)OR^{a2}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and C₆₋₁₀ aryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl is optionally substituted with 1 or 2 substituents independently selected from R²¹;

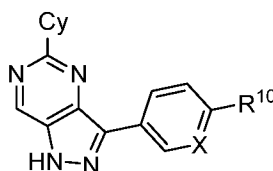
or any R^{c2} and R^{d2} attached to the same N atom, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{b2} is independently selected from C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R²¹ is independently selected from halo, D, CN, and OR^{a4}; and

each R^{a4} is C₁₋₆ alkyl.

45. The compound of claim 1, wherein the compound is a compound of Formula VI, or a pharmaceutically acceptable salt thereof:



VI

wherein:

X is selected from CH, CF, CCH₃ and N;

Cy is 4-12 membered heterocycloalkyl; wherein the 4-12 membered heterocycloalkyl 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 4-12 membered heterocycloalkyl is optionally substituted by oxo to form a carbonyl group; wherein when the 4-12 membered heterocycloalkyl of Cy has a fused aromatic ring, the 4-12 membered heterocycloalkyl is directly attached to the pyrazolopyrimidine core structure through a ring-forming atom of the saturated or partially saturated ring; and wherein the 4-12 membered heterocycloalkyl is optionally substituted with 1, 2 or 3 substituents independently selected from R²⁰;

R¹⁰ is selected from 4-10 membered heterocycloalkyl, wherein said 4-10 membered heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from R¹¹;

each R¹¹ is independently selected from C₁₋₆ alkyl, and 4-10 membered heterocycloalkyl, C₁₋₆ alkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R¹²;

each R¹² is independently selected from C₁₋₆ alkyl, C(O)OH, and OH;

each R²⁰ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, halo, CN, OR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, and C(O)OR^{a2}; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and C₆₋₁₀ aryl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{a2}, R^{c2} and R^{d2} is independently selected from H, C₁₋₆ alkyl and C₁₋₆ haloalkyl; wherein said C₁₋₆ alkyl is optionally substituted with 1 or 2 substituents independently selected from R²¹;

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 4-10 membered heterocycloalkyl group optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R^{b2} is independently selected from C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R²¹;

each R²¹ is independently selected from halo, D, CN, and OR^{a4}; and

each R^{a4} is C₁₋₆ alkyl.

46. The compound of claim 1, wherein the compound is selected from:
- 5-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)-3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine;
- (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)morpholine;
- 5-(7-azabicyclo[2.2.1]heptan-7-yl)-3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine;
- (1*R*,5*S*,6*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-8-azabicyclo[3.2.1]octan-6-ol;
- 1-((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)-2-methylpropan-1-one;
- 1-((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)-2-methoxyethan-1-one;
- (3*R*,5*S*)-*N*-isopropyl-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxamide;
- (3*R*,5*S*)-*N,N*,3,5-tetramethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxamide;
- ((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)(pyrrolidin-1-yl)methanone;
- ((3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazin-1-yl)(3-fluoropyrrolidin-1-yl)methanone;
- Ethyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate;
- 2-Fluoroethyl (3*R*,5*S*)-3,5-dimethyl-4-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)piperazine-1-carboxylate;
- Cyclopropyl((1*R*,5*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)methanone;
- ((1*R*,5*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)(pyrrolidin-1-yl)methanone;
- 4-((1*R*,5*S*)-8-(3-(6-((*R*)-3-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)benzonitrile; and
- 5-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine,

or a pharmaceutically acceptable salt thereof.

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

Methyl (3R,5S)-3,5-dimethyl-4-(3-(6-((R)-3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

(R)-5-(1-Methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)-3-(6-(3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine;

(R)-5-(3-Methyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-3-(6-(3-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidine;

(5-(3-(6-((R)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)(pyrrolidin-1-yl)methanone;

((1S,4S)-5-(3-(6-((R)-3-Methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)(pyrrolidin-1-yl)methanone

Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(4-(4-ethylpiperazin-1-yl)-3-methylphenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(methylcarbamoyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(1-methylpyrrolidin-3-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(4-(1-(2-hydroxyethyl)pyrrolidin-3-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(4-(4-(1-hydroxypropan-2-yl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

2-(4-(4-(5-((2R,6S)-4-(Methoxycarbonyl)-2,6-dimethylpiperazin-1-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)phenyl)piperazin-1-yl)-2-methylpropanoic acid;

Methyl (3R,5S)-3,5-dimethyl-4-(3-(6-((R)-2-methylmorpholino)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(6-((R)-3,4-dimethylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

Methyl (3R,5S)-4-(3-(4-((7S,8aR)-7-hydroxyhexahydroindolopyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,5-dimethylpiperazine-1-carboxylate;

1-Methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

1-Cyclopropyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

1,3-Dimethyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

3-Ethyl-1-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

6-(3-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

3-(1-Methyl-1H-pyrazol-4-yl)-5-(1-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1H-pyrazolo[4,3-d]pyrimidine;

5-(3-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine;

3-(1-Methyl-1H-pyrazol-4-yl)-5-(8-methyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-1H-pyrazolo[4,3-d]pyrimidine;

3-(1-Methyl-1H-pyrazol-4-yl)-5-(1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl)-1H-pyrazolo[4,3-d]pyrimidine;

9-(3-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[c]pyrazole;

1-(2,2-Difluoroethyl)-3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

1-Isopropyl-3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

1-(2-Methoxyethyl)-3-methyl-4-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperazin-2-one;

3-Methyl-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Ethyl-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-(2-Fluoroethyl)-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Isopropyl-8-(3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-((1R,4S)-4-Hydroxycyclohexyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

N,N-Dimethyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxamide;

8-(3-(1-(1-Isobutyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-Ethyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-Isopropyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-Cyclobutyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-Cyclopropyl-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

3-Methyl-8-(3-(1-(pyridin-3-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

4-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

3-Methyl-8-(3-(1-(2-methylpyridin-4-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3,8-diazabicyclo[3.2.1]octan-2-one;

8-(3-(1-(6-(Dimethylamino)pyridin-3-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

5-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)nicotinonitrile;

5-(4-(5-(3-Methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)picolinonitrile;

8-(3-(1-(Imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-4-yl)-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one;

2-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

3-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

2-Fluoro-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzonitrile;

N,N-Dimethyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide;

N-Methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide;

2-Fluoro-N-methyl-4-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)benzamide; and

N-Methyl-5-(4-(5-(3-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octan-8-yl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1H-pyrazol-1-yl)picolinamide;

or a pharmaceutically acceptable salt thereof.

48. A pharmaceutical composition comprising a compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

49. A method of inhibiting ALK2 activity, wherein said method comprising administering to a patient a compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof.

50. A method of treating a disease or disorder associated with inhibition of ALK2 interaction, wherein said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof.

51. A method of inhibiting FGFR activity, wherein said method comprising administering to a patient a compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof.

52. A method of treating a disease or disorder associated with inhibition of FGFR interaction, wherein said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof.

53. A method of treating a cancer in a patient, wherein said method comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof.

54. A method of treating myeloproliferative diseases in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, and ruxolitinib, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/052567

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07D487/04 A61K31/519
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/171405 A1 (ZHUO JINCONG [US] ET AL) 19 June 2014 (2014-06-19) claims 1,36,38	1-54
A	----- COREY R. HOPKINS: "Inhibitors of the bone morphogenetic protein (BMP) signaling pathway: a patent review (2008-2015)", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 26, no. 10, 4 August 2016 (2016-08-04), pages 1115-1128, XP055445439, ISSN: 1354-3776, DOI: 10.1080/13543776.2016.1217330 tables 3-4 ----- -/-	1-54



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

6 November 2019

Date of mailing of the international search report

14/11/2019

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/052567

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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