PYRIMIDINONES AS PI3K INHIBITORS

This application claims the benefit of priority of U.S. Prov. Appl. No. 61/221,160, filed on June 29, 2009, and U.S. Prov. Appl. No. 61/259,765, filed on November 10, 2009.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

The phosphoinositide 3-kinases (PI3Ks) belong to a large family of lipid signaling kinases that phosphorylate phosphoinositides at the D3 position of the inositol ring (Cantley, Science, 2002, 296(5573):1655-7). PI3Ks are divided into three classes (class I, II, and III) according to their structure, regulation and substrate specificity. Class I PI3Ks, which include PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, are a family of dual specificity lipid and protein kinases that catalyze the phosphorylation of phosphatidylinosito-4,5-bisphosphate (PIP_2) giving rise to phosphatidylinosito-3,4,5-trisphosphate (PIP_3). PIP_3 functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion and migration. All four class I PI3K isoforms exist as heterodimers composed of a catalytic subunit (p110) and a tightly associated regulatory subunit that controls their expression, activation, and subcellular localization. PI3Kα, PI3Kβ, and PI3Kδ associate with a regulatory subunit known as p85 and are activated by growth factors and cytokines through a tyrosine kinase-dependent mechanism (Jimenez, et al., J Biol Chem., 2002, 277(44):41556-62) whereas PI3Kγ associates with two regulatory subunits (p101 and p84) and its activation is driven by the activation of G-protein-coupled receptors (Brock, et al., J Cell Biol., 2003, 160(1):89-99). PI3Kα and PI3Kβ are ubiquitously expressed. In contrast, PI3Kγ and PI3Kδ are predominantly expressed in leukocytes (Vanhaesebroeck, et al., Trends Biochem Sci., 2005, 30(4):194-204).

The differential tissue distribution of the PI3K isoforms factors in their distinct biological functions. Genetic ablation of either PI3Kα or PI3Kβ results in embryonic lethality, indicating that PI3Kα and PI3Kβ have essential and non-redundant functions, at least during development (Vanhaesebroeck, et al., 2005). In contrast, mice which lack PI3Kγ and PI3Kδ are viable, fertile and have a normal life span although they show an altered immune system. PI3Kγ deficiency leads to impaired recruitment of macrophages and neutrophils to sites of inflammation as well as impaired T cell activation (Sasaki, et al., Science, 2000, 287(5455):1040-6). PI3Kδ-mutant mice have specific defects in B cell signaling that lead to impaired B cell development and reduced antibody responses after antigen stimulation (Clayton, et al., J. Exp. Med. 2002, 196(6):753-63; Jou, et al., Mol. Cell Biol. 2002, 22(24):8580-91; Okkenhaug, et al., Science, 2002, 297(5583):1031-4).

The phenotypes of the PI3Kγ and PI3Kδ-mutant mice suggest that these enzymes may play a role in inflammation and other immune-based diseases and this is borne out in preclinical models. PI3Kγ-mutant mice are largely protected from disease in mouse models of rheumatoid arthritis (RA) and asthma (Camps, et al., Nat Med. 2005, 11(9):936-43; Thomas, et al., Eur. J. Immunol., 2005, 35(4):1283-91). In addition, treatment of wild-type mice with a selective inhibitor of PI3Kγ was shown to reduce glomerulonephritis and prolong survival in the MRL-lpr model of systemic lupus nephritis (SLE) and to suppress joint inflammation and damage in models of RA (Barber, et al., Nat Med. 2005, 11(9):933-5; Camps, et al., 2005). Similarly, both PI3Kδ-mutant mice and wild-type mice treated with a selective inhibitor of PI3Kδ have been shown to have attenuated allergic airway inflammation and hyper-responsiveness in a mouse model of asthma (Ali, et al., Nature. 2004, 431(7011):1007-11; Lee, et al., FASEB J. 2006, 20(3):455-65) and to have attenuated disease in a model of RA (Randis, et al., Eur. J. Immunol., 2008, 38(5):1215-24).

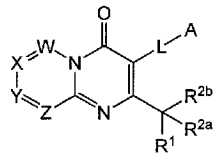
In addition to their potential role in inflammatory diseases, all four class I PI3K isoforms may play a role in cancer. The gene encoding p110α is mutated frequently in common cancers, including breast, prostate, colon and endometrial (Samuels, et al., Science, 2004, 304(5670):554; Samuels, et al., Curr. Opin. Oncol. 2006, 18(1):77-82). Eighty percent of these mutations are represented by one of three amino acid substitutions in the helical or kinase domains of the enzyme and lead to a significant upregulation of kinase activity resulting in oncogenic

transformation in cell culture and in animal models (Kang, et al., Proc. Natl. Acad. Sci. U.S.A. 2005, 102(3):802-7; Bader, et al., Proc. Natl. Acad. Sci. U.S.A. 2006, 103(5):1475-9). No such mutations have been identified in the other PI3K isoforms although there is evidence that they can contribute to the development and progression of malignancies. Consistent overexpression of PI3Kδ is observed in acute myeloblastic leukemia (Sujobert, et al., Blood, 2005, 106(3):1063-6) and inhibitors of PI3Kδ can prevent the growth of leukemic cells (Billottet, et al., Oncogene. 2006, 25(50):6648-59). Elevated expression of PI3Kγ is seen in chronic myeloid leukemia (Hickey, et al., J. Biol. Chem. 2006, 281(5):2441-50). Alterations in expression of PI3Kβ, PI3Kγ and PI3Kδ have also been observed in cancers of the brain, colon and bladder (Benistant, et al., Oncogene, 2000, 19(44):5083-90; Mizoguchi, et al., Brain Pathol. 2004, 14(4):372-7; Knobbe, et al., Neuropathol. Appl. Neurobiol. 2005, 31(5):486-90). Further, these isoforms have all been shown to be oncogenic in cell culture (Kang, et al., 2006).

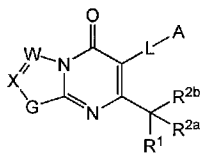
Thus, new or improved agents which inhibit kinases such as PI3K are continually needed for developing new and more effective pharmaceuticals that are aimed at augmentation or suppression of the immune and inflammatory pathways (such as immunosuppressive agents for organ transplants), as well as agents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

SUMMARY OF THE INVENTION

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



I



II

or pharmaceutically acceptable salts thereof, wherein constituent members are defined herein.

The present invention further provides pharmaceutical compositions comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention further provides methods of modulating an activity of one or more kinases (such as a PI3K) comprising contacting the kinase with a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating a disease or a disorder associated with abnormal kinase expression or activity in a patient by administering to a patient a therapeutically effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt of the same.

The present invention further provides methods of treating diseases such as immune-based diseases, cancer, and lung diseases in a patient by administering to the patient a therapeutically effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The present invention further provides a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, for use in therapy.

The present invention further provides use of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, for the production of a medicament for use in therapy.

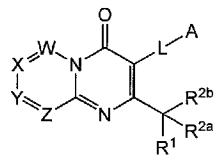
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. X-ray crystal structure of Example 15, step 5.

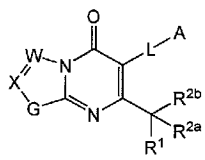
Figure 2. X-ray crystal structure lattice of Example 15, step 5.

DETAILED DESCRIPTION

The present invention provides, *inter alia*, compounds that modulate the activity of one or more PI3Ks and are useful, for example, in the treatment of various diseases such as those associated with expression or activity of one or more PI3Ks. The compounds of the invention include those of Formula I or II:



I



II

or pharmaceutically acceptable salts thereof, wherein:

A is C_{1-10} alkyl, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$;

L is absent, $(CR^{7a}R^{7b})_m$, $(CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)_2(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q$, or $(CR^{7a}R^{7b})_pNR^{7c}S(O)_2(CR^{7a}R^{7b})_q$;

W is N or CR^3;

X is N or CR^4;

Y is N or CR^5;

Z is N or CR^6;

G is O, S, or NR^N;

R^1 is OR^A, SR^A, $S(O)R^A$, $S(O)_2R^A$, NR^AR^B, $NR^CC(O)NR^AR^B$, $NR^CC(O)OR^A$, $NR^CC(=NR^E)NR^AR^B$, $NR^CS(O)_2R^A$, $NR^CS(O)_2NR^CR^A$, heterocycloalkyl, or heteroaryl, wherein the heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r\text{-}Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6}

haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^{2a} and R^{2b} are independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl ring or a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl ring, each optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^3, R^4, R^5, and R^6 are independently selected from H, halo, CN, NO_2, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$;

R^{7a} and R^{7b} are independently selected from H, halo, or C_{1-4} alkyl;

R^{7c} is H or C_{1-4} alkyl;

R^{7d} is H, CN, NO_2, OR^{a5}, SR^{b5}, $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, or $C(O)NR^{c5}R^{d5}$;

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4}$ alkyl$)_t$-Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^B and R^C are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^E is H, CN, NO_2, OR^{a5}, SR^{b5}, $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, or $C(O)NR^{c5}R^{d5}$;

R^N is H or C_{1-4} alkyl;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^a, R^b, R^c, and R^d are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl

is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c} and R^{d} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a1}, R^{b1}, R^{c1}, and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a2}, R^{b2}, R^{c2}, and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl,

C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a3}, R^{b3}, R^{c3}, and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{e} and R^{f} are independently selected from H, CN, NO_2, OR^{a5}, SR^{b5}, $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, and $C(O)NR^{c5}R^{d5}$;

R^{a5}, R^{b5}, R^{c5}, and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl,

cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4; and

r is 0 or 1.

In some embodiments, the compounds of the invention have Formula I.

In some embodiments, the compounds of the invention have Formula II.

In some embodiments, A is C_{1-10} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$,

and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^eS(O)R^b$, $NR^eS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments, L is absent.

In some embodiments, L is $(CR^{7a}R^{7b})_m$, $(CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)$ $(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)_2(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q$, or $(CR^{7a}R^{7b})_pNR^{7c}S(O)_2(CR^{7a}R^{7b})_q$.

In some embodiments, L is $(CR^{7a}R^{7b})_m$.

In some embodiments, W is N.

In some embodimetns, W is CR^3.

In some embodiments, X is N.

In some embodiments, X is CR^4.

In some embodiments, Y is N.

In some embodiments, Y is CR^5.

In some embodiments, Z is N.

In some embodiments, Z is CR^6.

In some embodiments, not more than 2 of W, X, Y, or Z are N.

In some embodiments, not more than 3 of W, X, Y, or Z are N.

In some embodiments, one of W and X is N.

In some embodiments, G is O.

In some embodiments, G is S.

In some embodiments, G is NR^N.

In some embodiments, R^1 is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r\text{-}Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, R^1 is NR^AR^B.

In some embodiments, R^{2a} and R^{2b} are independently selected from H and C_{1-6} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, at least one of R^{2a} and R^{2b} is other than H.

In some embodiments, R^3, R^4, R^5, and R^6 are independently selected from H or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments, R^3 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$,

$NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^{e})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e})NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments, R^4, R^5, and R^6 are each H.

In some embodiments, R^{7a}, R^{7b}, R^{7c}, and R^{7d} are each H.

In some embodiments, R^A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

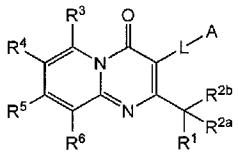
In some embodiments, R^B and R^C are independently selected from H and C_{1-6} alkyl.

In some embodiments, A is other than phenyl substituted at the 4-position by halogen.

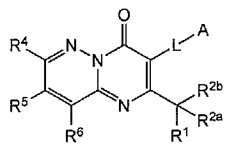
In some embodiments, r is 0.

In some embodiments, r is 1.

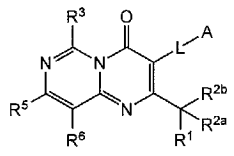
In some embodiments, the compounds of the invention have Formula Ia, Ib, Ic, Id, Ie, IIa, IIb, or IIc:



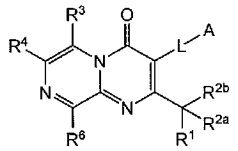
Ia



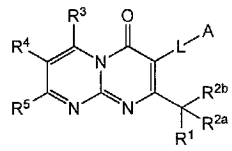
Ib



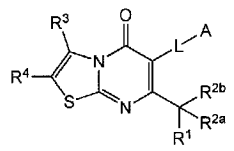
Ic



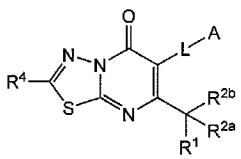
Id

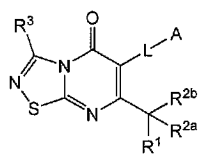


Ie



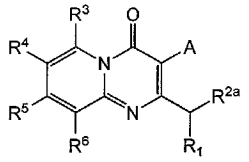
IIa

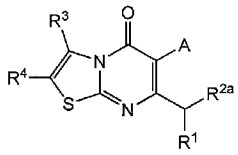




IIb IIc.

In some embodiments, the compounds of the invention have Formula If or IId:





If IId.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId:

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$;

R^1 is OR^A, SR^A, $S(O)R^A$, $S(O)_2R^A$, NR^AR^B, $NR^CC(O)NR^AR^B$, $NR^CC(O)OR^A$, $NR^CC(=NR^E)NR^AR^B$, $NR^CS(O)_2R^A$, $NR^CS(O)_2NR^CR^A$, heterocycloalkyl, or heteroaryl, wherein the heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r\text{-}Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^3, R^4, R^5, and R^6 are independently selected from H, halo, CN, NO_2, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$;

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4}$ alkyl$)_r$-Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^B and R^C are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl

is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^E is H, CN, NO_2, OR^{a5}, SR^{b5}, $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, or $C(O)NR^{c5}R^{d5}$;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^{e})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e})NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^a, R^b, R^c, and R^d are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^c and R^d together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a1}, R^{b1}, R^{c1}, and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl

is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a2}, R^{b2}, R^{c2}, and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a3}, R^{b3}, R^{c3}, and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl,

C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{e} and R^{f} are independently selected from H, CN, NO_2, OR^{a5}, SR^{b5}, $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, and $C(O)NR^{c5}R^{d5}$;

R^{a5}, R^{b5}, R^{c5}, and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy; and

r is 0 or 1.

In some embodiments of compounds of Formulas I and Ia-If, when A is 3-fluorophenyl; R^{2a} is H; R^3 is methyl; and R^4, R^5, and R^6 are H; then R^1 is other than 4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl.

In some embodiments of compounds of Formulas I and Ia-If, when A is 1,3-dioxolan-2-yl; R^{2a}, R^3, R^4, and R^6 are H; then R^1 is other than 1-(*tert*-butoxycarbonyl)piperidin-4-yl.

In some embodiments of compounds of Formulas I and Ia-If, R^1 is other than a substituted or unsubstituted pyrazolo[3,4-d]pyrimidin-1-yl group.

In some embodiments of compounds of Formulas I and Ia-If, R^1 is other than a substituted or unsubstituted piperidinyl group.

In some embodiments, the compound has Formula Ia.

In some embodiments, the compound has Formula Ib.

In some embodiments, the compound has Formula Ic.

In some embodiments, the compound has Formula Id.

In some embodiments, the compound has Formula Ie.

In some embodiments, the compound has Formula If.

In some embodiments, the compound has Formula IIa.

In some embodiments, the compound has Formula IIb.

In some embodiments, the compound has Formula IIc.

In some embodiments, the compound has Formula IId.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$,

$OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^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, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId,, A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$,

$NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is 6-membered heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is 5-membered heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is pyrazolyl optionally substituted with 1 or 2 substituents independently selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r\text{-}Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is bicyclic heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r\text{-}Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$,

$NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is purinyl optionally substituted with $-(C_{1-4}$ alkyl$)_r$-Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, or $S(O)_2NR^{c1}R^{d1}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is OR^A, SR^A, $S(O)R^A$, $S(O)_2R^A$, NR^AR^B, $NR^CC(O)NR^AR^B$, $NR^CC(O)OR^A$, $NR^CC(=NR^E)NR^AR^B$, $NR^CS(O)_2R^A$, or $NR^CS(O)_2NR^CR^A$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is NR^AR^B.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4}$ alkyl$)_r$-Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

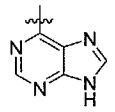
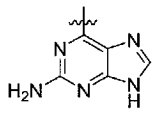
In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4}$ alkyl$)_r$-Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from $-(C_{1-4}$ alkyl$)_r$-Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$,

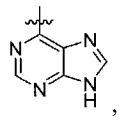
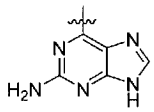
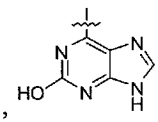
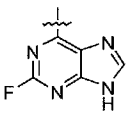
$NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

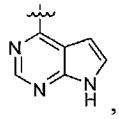
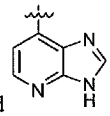
In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is:


or

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In some embodiments, R^A is selected from:


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, and

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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r$-$Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^B and R^C are independently selected from H and C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^B and R^C are each H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{1-6}

haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is methyl or ethyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is halo, CN, NO_2, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is H, halo, CN, NO_2, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, or C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is H or C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is methyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4, R^5, and R^6 are independently selected from H, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

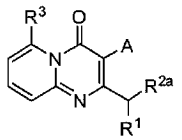
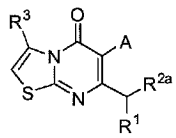
In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4, R^5, and R^6 are each H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4 is H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^5 is H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^6 is H.

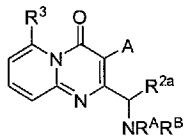
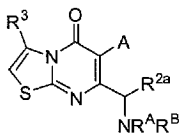
In some embodiments, the compounds of the invention have Formula Ig or IIe:

Ig IIe.

In some embodiments of compounds of Formulas Ig and IIe, R^1 is according to any of the previously recited embodiments for R^1.

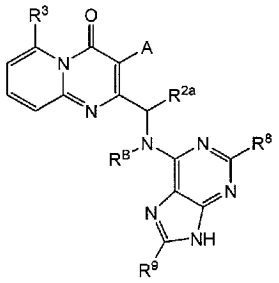
In some embodiments, the compounds of the invention have Formula Ih or IIf:

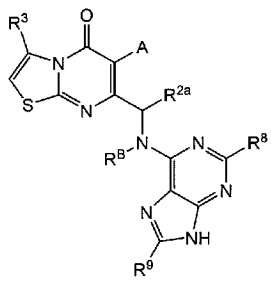



Ih IIf.

In some embodiments, of compounds of Formulas Ih and IIf, R^A is according to any of the previously recited embodiments for R^A.

In some embodiments, the compounds of the invention have Formula Ii or IIg:





Ii IIg.

wherein R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

In some embodiments, R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}S(O)_2R^{b5}$, and $NR^{c5}S(O)_2NR^{c5}R^{d5}$.

In some embodiments, R^8 and R^9 are independently selected from H and C_{1-6} alkyl.

In some embodiments of compounds of Formulas Ig-Ii and IIe-IIg, A is according to any of the previously recited embodiments for A.

In some embodiments of compounds of Formulas Ig-Ii and IIe-IIg, R^3 is according to any of the previously recited embodiments for R^3.

In some embodiments of compounds of Formulas Ig-Ii and IIe-IIg, R^{2a} is according to any of the previously recited embodiments for R^{2a}.

In some embodiments of compounds of Formulas Ig-Ii and IIe-IIg, R^B is according to any of the previously recited embodiments for R^B.

In some embodiments of compounds of Formula If or IId:

A is aryl or heteroaryl, each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, and OR^a;

R^1 is NR^AR^B or heteroaryl; wherein the hetereoaryl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, and OR^{a1};

R^{2a} is C_{1-6} alkyl;

R^3, R^4, R^5, and R^6 are independently selected from H, halo, CN, NO_2, OR^{a3}, and C_{1-6} alkyl; wherein the C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo;

R^A is heteroaryl, which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, CN, OR^{a1}, and $NR^{c1}R^{d1}$;

R^B is H;

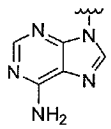
each R^a is independently selected from H and C_{1-6} alkyl;

each R^{a1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo; and

each R^{a3} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo.

In some embodiments of compounds of Formula If or IId:

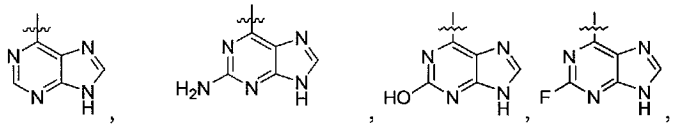
A is phenyl, 5-membered heteroaryl or 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, and OR^a;

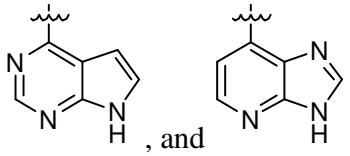
R^1 is NR^AR^B or  ;

R^{2a} is C_{1-6} alkyl;

R^3, R^4, R^5, and R^6 are independently selected from H, halo, CN, NO_2, OR^{a3}, and C_{1-6} alkyl; wherein the C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo;

R^A is selected from:





, and ;

R^B is H;

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

each R^{a3} is independently selected from H and C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo.

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. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, linking substituents are described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example, -NR(CR'R'')$_n$- includes both -NR(CR'R'')$_n$- and -(CR'R'')$_n$NR-. Where the structure clearly 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 "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, sec-butyl, t-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, sec-pentyl, neopentyl). An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

As used herein, “alkenyl” refers to an alkyl group having one or more carbon-carbon double bonds. Example alkenyl groups include ethenyl, propenyl, cyclohexenyl.

As used herein, “alkynyl” refers to an alkyl group having one or more carbon-carbon triple bonds. Example alkynyl groups include ethynyl, propynyl.

As used herein, “haloalkyl” refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5.

As used herein, “halosulfanyl” refers to a sulfur group having one or more halogen substituents. Example halosulfanyl groups include pentahalosulfanyl groups such as SF_5.

As used herein, “aryl” refers to monocyclic or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

As used herein, “cycloalkyl” refers to non-aromatic cyclic hydrocarbons including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) groups and spirocycles. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido. Cycloalkyl groups also include cycloalkylidenes. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclopentene, cyclohexane. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring.

As used herein, “heteroaryl” refers to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (*e.g.*, having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-

thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl. Examples of bicyclic heteroaryl groups include without limitation, purinyl, indolyl. In some embodiments, any ring-forming N in a heteroaryl moiety can be substituted by oxo. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 9 to about 10, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, "heterocycloalkyl" refers to non-aromatic heterocycles having one or more ring-forming heteroatoms such as an O, N, or S atom. Heterocycloalkyl groups include monocyclic and polycyclic (*e.g.*, having 2, 3 or 4 fused rings) systems as well as spirocycles. Example "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido. 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 nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl, and benzo derivatives of heterocycles. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. The 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. In some embodiments, the heterocycloalkyl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double or triple bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double or triple bonds.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

As used herein, "arylalkyl" refers to alkyl substituted by aryl and "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. An example arylalkyl group is benzyl.

As used herein, “heteroarylalkyl” refers to alkyl substituted by heteroaryl and “heterocycloalkylalkyl” refers to alkyl substituted by heterocycloalkyl.

As used herein, “amino” refers to NH_2.

As used herein, “alkoxy” refers to an –O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), t-butoxy.

As used herein, “haloalkoxy” refers to an –O-(haloalkyl) group.

As used herein, “alkylthio” refers to an –S-alkyl group. Example alkylthio groups include meththio, ethylthio, propylthio (*e.g.*, n-propylthio and isopropylthio).

As used herein, “alkylamino” refers to an –NH-alkyl group. Example alkylamino groups include methylamino, ethylamino, propylamino (*e.g.*, n-propylamino and isopropylamino).

As used herein, “di(alkyl)amino” refers to an $–N(alkyl)_2$ group. Example di(alkyl)amino groups include dimethylamino, diethylamino, dipropylamino (*e.g.*, di(n-propyl)amino and di(isopropyl)amino).

It should be 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. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

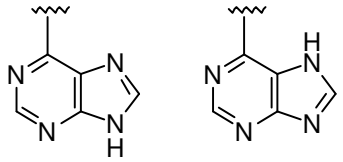
The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically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

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a chiral

resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane.

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

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. For example, purine includes the *9H* and a *7H* tautomeric forms:



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

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

The term, "compound," as used herein is meant to include all stereoisomers, geometric iosomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by

name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

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

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By “substantially isolated” is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope 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, for example, a temperature from about 20 ºC to about 30 ºC.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by

reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977).

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.

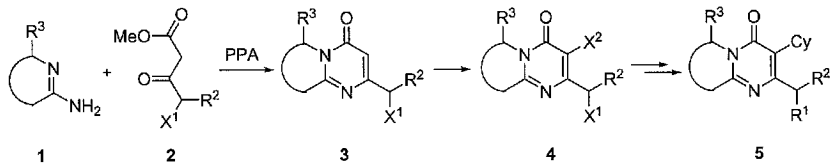
The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at 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 can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., Wiley & Sons, Inc., New York (1999).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

Example synthetic methods for preparing compounds of the invention are provided in the Schemes below. For instance, compounds of the invention can be prepared by the general synthetic procedure shown in Scheme 1. Heteroaryl compounds of formula 1 can react with 4-halo-3-oxo-pentanoates **2** in the presence of polyphosphoric acid (PPA) to provide the compounds of formula **3** via a cyclocondensation reaction. These can be subjected to halogenation reaction under suitable conditions, to provide halogenated compounds **4**. Compounds of formula **4** can be transformed to the compounds of formula **5** through any variation of a sequence of steps. X^1 can be replaced with either an azide, an amine, or a heterocyclic group through an S_N2 displacement and eventually transformed to the R^1 group. X^2 can be converted to a desired cyclic moiety (Cy) through any of the standard cross-coupling reactions, known to one skilled in the art, e.g., using boronic acid derivatives of the desired cyclic moiety.

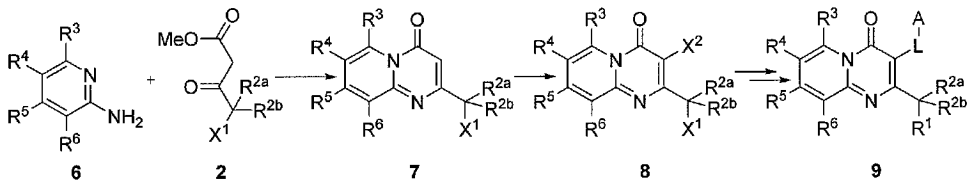
Scheme 1



1 **2** **3** **4** **5**

As shown in Scheme **2**, the pyrido[1,2-a]pyrimidin-4-ones of the invention can be prepared by cyclocondensation of aminopyrimidines **6** with a β-keto ester **2**. Halogenation of the resultant pyridopyridinones **7** under suitable conditions (such as NBS or bromine) provides compounds of formula **8**. The latter can be transformed to the compounds of formula **9** through an S_N2 subsitution of X^1 with a hetereocycle R^1 followed by a coupling reaction of X^2 with L-A moiety (such as a Negishi coupling of organozinc reagent; a Suzuki or Stille coupling of an arylboronic acid or arylstanne, respectively). Alternatively, X^1 can be replaced with either an amine or an azide which can be reduced to amine. The amine can then be subjected to coupling reaction with a R^1 moiety to give compounds of formula **9**.

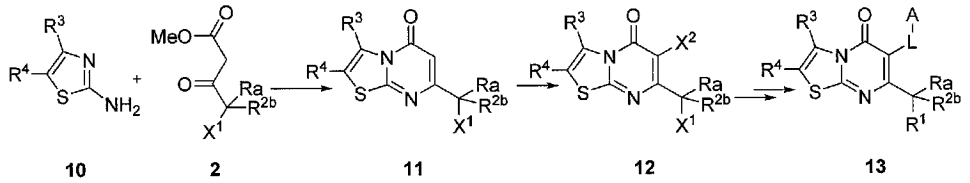
Scheme 2



6 2 7 8 9

The thiazolo[3,2-a]pyrimidin-5-ones of the invention can be prepared according to Scheme 3. 2-Aminothiazole **10** condensed with a β-keto ester **2** provides thiazolopyrimidinone **11**. Compounds of formula **11** can be converted to compounds of formula **13** through any variations of a sequence of steps as described above.

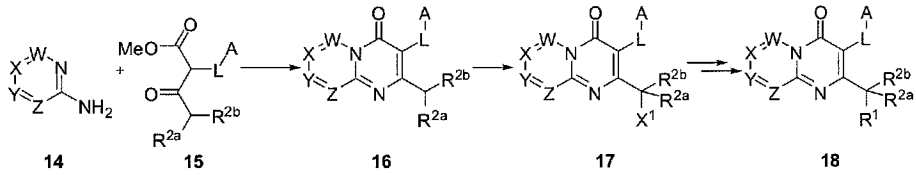
Scheme 3



10 2 11 12 13

Alternatively, compounds of the invention can be synthesized by reacting amino heterocycles **14** with an α-substituted β-keto ester **15** shown in Scheme **4**. The cyclocondensation derivatives **16** can then be subjected to halogenation (such as NBS or bromine) or oxidation (such as SeO_2) to afford halogen compounds **17** (X^1 = halogen), or alcohol compounds **17** (X = OH), respectively. Compounds of formula **17** can then be transformed to compounds of formula **18** through any variations of a sequence of steps. X^1 can be coupled directly with a heterocycles under any of the cross coupling conditions know to one skilled in the art (such as Buchwald-Hartwig cross coupling conditions) or converted to a halogen then the latter can be coupled with a heterocycles through S_N2 substitutions.

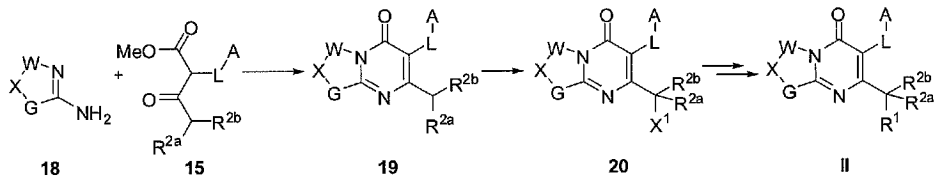
Scheme 4



14 15 16 17 18

Compounds of Formula II of the invention can be prepared according to Scheme 5. Amino heterocycles **19** condensed with α-substituted β-ketone ester **15** affords compounds of formula **20**. The latter can be transformed to compounds of Formula II through any variation of steps described above.

Scheme 5



18 15 19 20 II

It should noted that in all of the Schemes described herein, if there are functional groups present on a substituent group, further modification can be made if appropriate and desired. For example, a CN group can be hydrolyzed to afford an amide group; a carboxylic acid can be converted to a ester, which in turn can be reduced to an alcohol, which in turn can be further modified. In another example, an OH group can be converted into a better leaving group such as mesylate, which in turn is suitable for nucleophilic substitution, such as by CN. Furthermore, an OH group can be subjected to Mitsunobu reaction conditions with phenol, or hetereoaryl alcohol, to afford aryl or heteroaryl ether compounds. One skilled in the art will recognize further modifications.

It should be further noted that the reaction sequences described above can be modified to suit different target molecules. For instance, Cy-boronic acid can be reacted with **4** to generate

the Suzuki product first. The X^1 group of the Suzuki product can then be further functionalized with a nucleophilic reagent such as an azide or a heterocyclic amine.

Methods

The compounds of the invention can modulate activity of one or more of various kinases including, for example, phosphoinositide 3-kinases (PI3Ks). The term "modulate" is meant to refer to an ability to increase or decrease the activity of one or more members of the PI3K family. Accordingly, the compounds of the invention can be used in methods of modulating a PI3K by contacting the PI3K with any one or more of the compounds or compositions described herein. In some embodiments, compounds of the present invention can act as inhibitors of one or more PI3Ks. In further embodiments, the compounds of the invention can be used to modulate activity of a PI3K in an individual in need of modulation of the receptor by administering a modulating amount of a compound of the invention, or a pharmaceutically acceptable salt thereof. In some embodiments, modulating is inhibiting.

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

Kinases to which the present compounds bind and/or modulate (e.g., inhibit) include any member of the PI3K family. In some embodiments, the PI3K is PI3Kα, PI3Kβ, PI3Kγ, or PI3Kδ. In some embodiments, the PI3K is PI3Kγ or PI3Kδ. In some embodiments, the PI3K is PI3Kγ. In some embodiments, the PI3K is PI3Kδ. In some embodiments, the PI3K includes a mutation. A mutation can be a replacement of one amino acid for another, or a deletion of one or more amino acids. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

In some embodiments, more than one compound of the invention is used to inhibit the activity of one kinase (e.g., PI3Kγ or PI3Kδ).

In some embodiments, more than one compound of the invention is used to inhibit more than one kinase, such as at least two kinases (e.g., PI3Kγ and PI3Kδ).

In some embodiments, one or more of the compounds is used in combination with another kinase inhibitor to inhibit the activity of one kinase (e.g., PI3Kγ or PI3Kδ).

In some embodiments, one or more of the compounds is used in combination with another kinase inhibitor to inhibit the activities of more than one kinase (e.g., PI3Kγ or PI3Kδ), such as at least two kinases.

The compounds of the invention can be selective. By "selective" is meant that the compound binds to or inhibits a kinase with greater affinity or potency, respectively, compared to at least one other kinase. In some embodiments, the compounds of the invention are selective inhibitors of PI3Kγ or PI3Kδ over PI3Kα and/or PI3Kβ. In some embodiments, the compounds of the invention are selective inhibitors of PI3Kδ (*e.g.*, over PI3Kα, PI3Kβ and PI3Kγ). In some embodiments, the compounds of the invention are selective inhibitors of PI3Kγ (*e.g.*, over PI3Kα, PI3Kβ and PI3Kδ). In some embodiments, selectivity can be at least about 2-fold, 5-fold, 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 200-fold, at least about 500-fold or at least about 1000-fold. Selectivity can be measured by methods routine in the art. In some embodiments, selectivity can be tested at the K_m ATP concentration of each enzyme. In some embodiments, the selectivity of compounds of the invention can be determined by cellular assays associated with particular PI3K kinase activity.

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

abnormal activity of PI3K. In some embodiments, the disease is characterized by mutant PI3K. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

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

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

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

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

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

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

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

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

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

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

As used herein, the term "treating" or "treatment" refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

Combination Therapies

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

Example antibodies for use in combination therapy include Trastuzumab (e.g. anti-HER2), Ranibizumab (e.g. anti-VEGF-A), Bevacizumab (trade name Avastin, e.g. anti-VEGF, Panitumumab (e.g. anti-EGFR), Cetuximab (e.g. anti-EGFR), Rituxan (anti-CD20) and antibodies directed to c-MET.

One or more of the following agents may be used in combination with the compounds of the present invention and are presented as a non limiting list: a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, temozolomide, cyclophosphamide, SCH

66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec™, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17.alpha.-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant, Ifosfomide, Rituximab, C225, Campath, Clofarabine, cladribine, aphidicolon, rituxan, sunitinib, dasatinib, tezacitabine, Sml1, fludarabine, pentostatin, triapine, didox, trimidox, amidox, 3-AP, and MDL-101,731.

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

Example steroids include corticosteroids such as dexamethasone or prednisone.

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

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

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

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

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

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

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

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

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated.

Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, and thickeners may be necessary or desirable. Coated condoms, and gloves may also be useful.

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

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

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation

types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art, e.g., see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: 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.

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

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

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

In some embodiments, the compounds or compositions of the invention contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 to about 550,

about 550 to about 600, about 600 to about 650, about 650 to about 700, about 700 to about 750, about 750 to about 800, about 800 to about 850, about 850 to about 900, about 900 to about 950, or about 950 to about 1000 mg of the active ingredient.

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

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

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

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

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions 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, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g. glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose. 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, for example, 100 g which are optionally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

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

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization

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

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a 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.

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

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating PI3K in tissue samples, including human, and for identifying PI3K ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes PI3K assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* PI3K labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

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

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

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

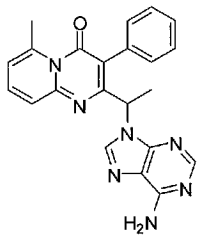
The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of PI3K-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound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

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

EXAMPLES

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

Example 1. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one



Step 1. methyl 4-chloro-3-oxopentanoate

To a solution of 3-oxopentanoic acid, methyl ester (Aldrich, 26.0 mL, 207.2 mmol) in methylene chloride (300 mL) was added in portions, N,N,N-trimethyl(phenyl) methanaminium dichloroiodanuide (75.71 g, 217.5 mmol). The reaction mixture was stirred at room temperature (rt) for 2 h, then washed with saturated sodium thiosulfate, brine, dried over magnesium sulfate and concentrated. The crude product was used directly in next step (23 g, 67.4%).

Step 2. 2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a manually stirred polyphosphoric acid (30 g, 200 mmol) in a 200 mL beaker was added 6-methyl-2-pyridinamine (Aldrich, 4.7 g, 43 mmol), followed by methyl 4-chloro-3-oxopentanoate (8.584 g, 52.15 mmol). The mixture was heated with stirring at 110 °C for 5 h. After being cooled, the dark slurry was transferred on to 100 g of ice. The pH of the mixture was adjusted to 6-7 with 10% sodium hydroxide. The mixture was extracted with methylene chloride. The combined organic layers were washed with water, brine, dried over magnesium sulfate and evaporated to dryness. The residue was purified on silica gel, eluting with 0-10% methanol in methylene chloride, to yield the desired product (3.16 g, 32.7%). LCMS calculated for $C_{11}H_{12}ClN_2O(M+H)^+$: m/z = 223.1; Found: 223.2.

Step 3. 3-bromo-2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a stirred solution of 2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.16 g, 14.2 mmol) in methylene chloride (30 mL) was added drop-wise bromine (0.804 mL, 15.6 mmol) in methylene chloride (7 mL). The reaction mixture was stirred at room temperature for 2 h. The product precipitated out and was collected by filtration (2.42 g, 56.6%). LCMS calculated for $C_{11}H_{11}BrClN_2O(M+H)^+$: m/z = 301.0; Found: 301.1.

Step 4. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-3-bromo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

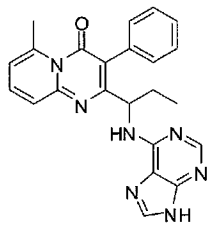
A mixture of 3-bromo-2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (1.24 g, 4.11 mmol), adenine (Sigma, 1.08 g, 8.04 mmol), and potassium carbonate (1.11 g, 8.04 mmol) in *N,N*-dimethylformamide (20 mL) was stirred at room temperature overnight. The suspension was then poured into water and extracted with methylene chloride. The combined

organic layers were washed with water, brine, and then the organic layers dried and evaporated to dryness. The residue was chromatographed on silica gel, eluting with 0 to 10% MeOH in methylene chloride, to provide the desired product (176 mg, 10.7%). LCMS calculated for $C_{16}H_{15}BrN_7O(M+H)^+$: m/z = 400.1; Found: 400.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.44 (1H, s), 8.07 (1H, s), 7.67 (1H, dd, J = 8.7 and 7.2 Hz), 7.30 (1H, br d, J = 8.7 Hz), 7.20 (2H, s), 6.99 (1H, br d, J = 7.2 Hz), 6.15 (1H, q, J = 7.2 Hz), 2.91 (3H, s), 1.84 (3H, d, J = 7.2 Hz) ppm.

Step 5. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 2-[1-(6-amino-9H-purin-9-yl)ethyl]-3-bromo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.075 mmol) and phenylboronic acid (11.0 mg, 0.0899 mmol) in 1,4-dioxane (0.6 mL) was added a 1 M solution of sodium carbonate (9.53 mg, 0.0899 mmol) in water (0.089 mL) and tetrakis(triphenylphosphine)palladium (0) (4.33 mg, 0.00375 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 10 (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the desired product. LCMS calculated for $C_{22}H_{20}N_7O(M+H)^+$: m/z = 398.2; Found: 398.3. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.37 (1H, s), 7.97 (1H, s), 7.56 (1H, dd, J = 8.7 and 6.6 Hz), 7.41–7.36 (5H, m), 7.26 (1H, br d, J = 9.0 Hz), 7.09 (2H, br s), 6.85 (1H, br d, J = 7.2 Hz), 5.59 (1H, q, J = 7.2 Hz), 2.80 (3H, s), 1.64 (3H, d, J = 7.2 Hz) ppm.

Example 2. 6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



Step 1. methyl 4-bromo-3-oxohexanoate

Under a nitrogen atmosphere, a solution of bromine (8.61 mL, 167 mmol) in chloroform (20 mL) was added drop-wise over a period of 2 h to a solution of methyl 3-oxohexanoate (Fluka, 24.1 g, 167 mmol) in chloroform (147 mL), at 0 °C (ice bath). The reaction mixture was stirred for 30 min at 0 °C and then allowed to warm to room temperature overnight. While stirring, a stream of air was bubbled through the solution for 1 hour. The reaction mixture was dried over sodium sulfate and the solvent evaporated under reduced pressure to provide the desired compound.

Step 2. 2-(1-bromopropyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a manually stirred polyphosphoric acid (80 g, 800 mmol) in a 1000 mL beaker at room temperature was added 6-methyl-2-pyridinamine (15 g, 140 mmol), followed by methyl 4-bromo-3-oxohexanoate (37.3 g, 167 mmol). The mixture was heated with stirring at 110 °C for 5 h. After cooling, the dark slurry was transferred into 300 g of ice. The pH of the mixture was adjust to 6-7 with 10% sodium hydroxide. The precipitate was collected by filtration under reduced pressure, washed with water, and air dried to yield the desired product (25.4 g, 64.8%). LCMS calculated for $C_{12}H_{14}BrN_2O(M+H)^+$: m/z = 281.0; Found: 281.2. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.66 (1H, d, J = 9.0 and 6.9 Hz), 7.39 (1H, d, J = 9.0 Hz), 6.90 (1H, d, J = 6.9 Hz), 6.33 (1H, s), 4.91 (1H, t, J = 7.5 Hz), 2.91 (3H, s), 2.15 (2H, qd, J = 7.5 and 7.5 Hz), 0.93 (3H, t, J = 7.5 Hz) ppm.

Step 3. 2-(1-bromopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 2-(1-bromopropyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.46 g, 12.3 mmol) and *N*-iodosuccinimide (4.15 g, 18.4 mmol) in acetonitrile (100 mL) was stirred at 80 °C, under nitrogen, overnight. After removal of acetonitrile in vacuum, the resulting solid was dissolved in methylene chloride, washed with water, saturated $Na_2S_2O_3$, saturated sodium bicarbonate, and brine; and then the organic layers dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to provide the desired product (4.53 g, 90.4%). LCMS calculated for $C_{12}H_{13}BrIN_2O(M+H)^+$: m/z = 406.9; Found: 407.1.

Step 4. 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 2-(1-bromopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (4.50 g, 11.0 mmol) and sodium azide (3.59 g, 55.3 mmol) in DMF was stirred at room temperature for 2 h. After diluting with ethyl acetate, the mixture was washed with water, brine, dried over sodium sulfate, and evaporated under reduced pressure to provide the crude product, which was used directly in next step (3.35 g, 82.1%). LCMS calculated for $C_{12}H_{13}IN_5O(M+H)^+$: m/z = 370.0; Found: 370.2.

Step 5. 2-(1-azidopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.11 g, 0.29 mmol) and phenylboronic acid (42.9 mg, 0.352 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (37.3 mg, 0.352 mmol) in water (0.35 mL) and tetrakis(triphenylphosphine)palladium (0) (16.9 mg, 0.0147 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to provide the desired product (50 mg, 53.4%). LCMS calculated for $C_{18}H_{18}N_5O(M+H)^+$: m/z = 320.2; Found: 320.3.

Step 6. 2-(1-aminopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

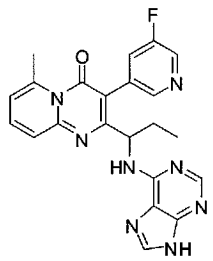
To a stirred solution of 2-(1-azidopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.094 mmol) in tetrahydrofuran (0.24 mL) and water (0.06 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.11 mL) at room temperature and the mixture was stirred at room temperature for 1 hour. To the mixture was added methylene chloride and the mixture was washed with brine, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The crude residue was used directly in next step. LCMS calculated for $C_{18}H_{20}N_3O(M+H)^+$: m/z = 294.2; Found: 294.3.

Step 7. 6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 6-bromo-9H-purine (Aldrich, 0.0152 g, 0.07656 mmol), 2-(1-aminopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.019 g, 0.064 mmol), and *N,N*-diisopropylethylamine (0.0134 mL, 0.07666 mmol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was cooled and purified on RP-HPLC at pH 10 (XBridge C18

column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the product as the free base. LCMS calculated for $C_{23}H_{22}N_7O(M+H)^+$: m/z = 412.2; Found: 412.4. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.07 (2H, m), 7.60 (1H, dd, J = 9.0 and 6.9 Hz), 7.39–7.32 (7H, m), 7.00 (1H, m), 6.85 (1H, br d, J = 6.9 Hz), 5.13 (1H, m), 2.81 (3H, s), 1.72 (2H, m), 0.65 (3H, t, J = 7.2 Hz) ppm.

Example 3. 3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



Step 1. 2-(1-aminopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a stirred solution of 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.10 g, 8.40 mmol) in tetrahydrofuran (20 mL) and water (6.06 mL) was added a 1.0 M solution of trimethylphosphine in tetrahydrofuran (0.1 mmol) at room temperature and stirred for 1 hour. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (2.58 g, 89.5%). LCMS calculated for $C_{12}H_{15}IN_3O(M+H)^+$: m/z = 344.0; Found: 344.2.

Step 2. 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

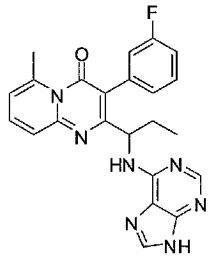
A mixture of 6-bromo-9H-purine (1.65 g, 0.008270 mol), 2-(1-aminopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (2.58 g, 0.00752 mol), and *N,N*-diisopropylethylamine (1.571 mL, 0.009022 mol) in ethanol (60 mL) was refluxed under nitrogen overnight. The

mixture was concentrated and the resulting residue was purified on silica gel, eluting with 0 to 10% methanol in methylene chloride, to provide the desired product (2.86 g, 82.5%). LCMS calculated for $C_{17}H_{17}IN_7O(M+H)^+$: m/z = 462.1; Found: 462.2. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (2H, m), 8.19 (1H, s), 8.15 (1H, s), 7.69 (1H, dd, J = 8.7 and 6.9 Hz), 7.44 (1H, d, J = 8.7 Hz), 6.99 (1H, d, J = 6.9 Hz), 5.69 (1H, m), 2.89 (3H, s), 1.91 (2H, m), 0.95 (3H, t, J = 7.2 Hz) ppm.

Step 3. 3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.065 mmol) and (5-fluoropyridin-3-yl)boronic acid (Combi-Blocks, 11.0 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the desired product. LCMS calculated for $C_{22}H_{20}FN_8O(M+H)^+$: m/z = 431.2; Found: 431.3.

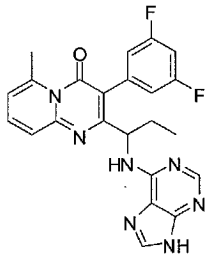
Example 4. 3-(3-fluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (3-fluorophenyl)boronic acid (Aldrich, 10.9 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of

sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the desired product. LCMS calculated for $C_{23}H_{21}FN_7O(M+H)^+$: m/z = 430.2; Found: 430.3. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.11 (2H, m), 7.65 (1H, m), 7.45 (2H, m), 7.24 (4H, m), 7.08 (1H, m), 6.91 (1H, m), 5.17 (1H, m), 2.87 (3H, s), 1.79 (2H, m), 0.72 ((3H, t, J = 7.2 Hz) ppm. ^{19}F NMR (DMSO-d_6, 282 MHz) δ –114 ppm.

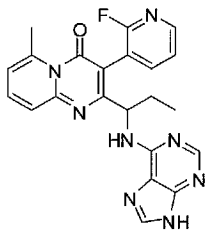
Example 5. 3-(3,5-difluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (3,5-difluorophenyl)boronic acid (Aldrich, 12.3 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the desired product. LCMS calculated for $C_{23}H_{20}F_2N_7O(M+H)^+$: m/z = 448.2; Found: 448.3. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.06 (2H,

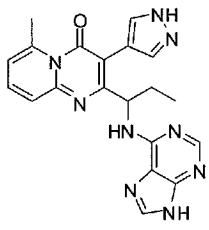
m), 7.61 (1H, m), 7.38 (1H, m), 7.14 (5H, m), 6.88 (1H, m), 5.08 (1H, m), 2.83 (3H, s), 1.75 (2H, m), 0.70 ((3H, t, J = 7.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 282 MHz) δ –111 ppm.

Example 6. 3-(2-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



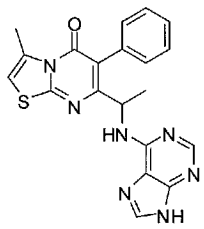
To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (2-fluoropyridin-3-yl)boronic acid (Alfa Aesar, 11.0 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 2 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to provide the desired product as a TFA salt. LCMS calculated for free base $C_{22}H_{20}FN_8O(M+H)^+$: m/z = 431.2; Found: 431.3.

Example 7. 6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-3-(1H-pyrazol-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one



To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (Aldrich, 15.1 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 2 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to provide the desired product as a TFA salt. LCMS calculated for free base $C_{20}H_{20}N_9O(M+H)^+$: m/z = 402.2; Found: 402.1.

Example 8. 3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. methyl 4-bromo-3-oxopentanoate

Under a nitrogen atmosphere, a solution of bromine (8.61 mL, 167 mmol) in chloroform (20 mL, 200 mmol) was added dropwise over a period of 2 h to a solution of 3-oxopentanoic acid, methyl ester (Aldrich, 21.0 mL, 167 mmol) in chloroform (147 mL, 1840 mmol), at 0 °C (ice bath). The reaction mixture was stirred for 30 min at 0 °C and then allowed to stand at room temperature overnight. While stirring, a stream of air was bubbled through the solution for 1 hour. After drying over sodium sulfate, the solvent was evaporated under reduced pressure leaving the desired compound.

Step 2. 7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a manually stirred polyphosphoric acid (80 g, 800 mmol) in a 1000 mL beaker was added 4-methyl-1,3-thiazol-2-amine (Aldrich, 16 g, 140 mmol), followed by methyl 4-bromo-3-

oxopentanoate (34.9 g, 167 mmol). The mixture was heated with stirring at 110 °C for 5 h. After cooling, the dark slurry was transferred into 300 g of ice. The pH of the mixture was adjust to 6-7 with 10% sodium hydroxide. The aqueous layer was discarded and the dark oil layer was diluted with methylene chloride and washed with 1 N NaOH, brine, dried over magnesium sulfate, and evaporated to dryness to yield the desired product (16.2 g, 42.6%). LCMS calculated for $C_9H_{10}BrN_2OS(M+H)^+$: m/z = 273.0; Found: 273.1.

Step 2. 6-bromo-7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (16.2 g, 59.3 mmol) and *N*-bromosuccinimide (15.8 g, 89.0 mmol) in acetonitrile (500 mL) was stirred at 80 °C, under nitrogen, overnight. After removal of acetonitrile in vacuum, the resulting solid was dissolved in methylene chloride, washed with water, saturated $Na_2S_2O_3$, saturated sodium bicarbonate, and brine; and then the organic layers dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to provide the desired product (19.5 g, 93.4%). LCMS calculated for $C_9H_9Br_2N_2OS(M+H)^+$: m/z = 350.9; Found: 351.0.

Step 3. 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (11.1 g, 31.5 mmol) and sodium azide (6.15 g, 94.6 mmol) in dimethyl formamide (DMF) (100 mL) was stirred at room temperature for 2 h. After diluting with EtOAc, the mixture was washed with water, brine, dried over sodium sulfate, and evaporated under reduced pressure. The crude residue was purified on silica gel, eluting with 0 to 80% EtOAc in hexane, to provide the product (8.68 g, 87.6%). LCMS calculated for $C_9H_9BrN_5OS(M+H)^+$: m/z = 314.0; Found: 313.9. ^1H NMR (DMSO-d_6, 300 MHz) δ 7.15 (1H, s), 4.83 (1H, q, J = 6.6 Hz), 2.69 (3H, s), 1.48 (3H, d, J = 6.6 Hz) ppm.

Step 4. 7-(1-azidoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.100 g, 0.318 mmol) and phenylboronic acid (46.6 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was

heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with 0 to 50% EtOAc in hexane, to provide the desired product (44 mg, 44.4%). LCMS calculated for $C_{15}H_{14}N_5OS(M+H)^+$: m/z = 312.1; Found: 312.3.

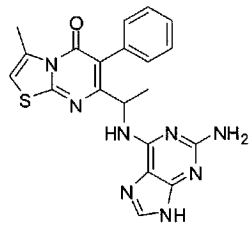
Step 5. 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.044 g, 0.14 mmol) in tetrahydrofuran (0.4 mL) and water (0.102 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.17 mL) at room temperature and the mixture was stirred at room temperature for 1 hour. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (36 mg, 89.3%). LCMS calculated for $C_{15}H_{16}N_3OS(M+H)^+$: m/z = 286.1; Found: 286.0.

Step 6. 3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

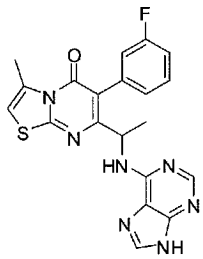
A mixture of 6-bromo-9H-purine (0.01504 g, 0.0076 mmol), 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.018 g, 0.063 mmol), and *N,N*-diisopropylethylamine (0.013 mL, 0.0076 mol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for free base $C_{20}H_{18}N_7OS(M+H)^+$: m/z = 404.1; Found: 404.3. ^{1}H NMR (DMSO-d_6, 300 MHz) for a TFA salt: δ 8.54 (2H, m), 8.41 (2H, m), 7.44–7.36 (5H, m), 7.08 (1H, d, J = 1.2 Hz), 5.21 (1H, m), 2.64 (3H, s), 1.38 (3H, d, J = 6.6 Hz) ppm.

Example 9. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 2-amino-6-bromopurine (Aldrich, 0.01618 g, 0.007558 mmol), 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 5; 0.018 g, 0.063 mmol), and *N,N*-diisopropylethylamine (0.01318 mL, 0.007569 mmol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resulting residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{19}N_8OS(M+H)^+$: m/z = 419.1; Found: 419.3. ^{1}H NMR (DMSO-d_6, 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.46–7.33 (6H, m), 7.14–7.11 (3H, m), 5.20 (1H, m), 2.66 (3H, d, *J* = 1.5 Hz), 1.32 (3H, d, *J* = 6.6 Hz) ppm.

Example 10. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 3; 0.100 g, 0.318 mmol) and (3-fluorophenyl)boronic acid (53.4 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159

mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with 0 to 50% EtOAc in hexane, to provide the desired product (35 mg, 33.4%). LCMS calculated for $C_{15}H_{13}FN_5OS(M+H)^+$: m/z = 330.1; Found: 330.2.

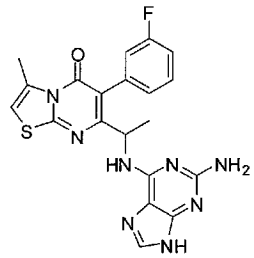
Step 2. 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a stirred solution of 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.037 g, 0.11 mmol) in tetrahydrofuran (0.3 mL) and water (0.0811 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.13 mmol) at room temperature and stirred for 1 hour. To the mixture was added EtOAc and was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (31 mg, 90.9%). LCMS calculated for $C_{15}H_{15}FN_3OS(M+H)^+$: m/z = 304.1; Found: 304.3.

Step 3. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

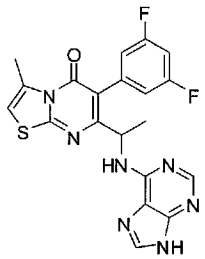
A mixture of 6-bromo-9H-purine (0.01258 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.016 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.011 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resulting residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{17}FN_7OS(M+H)^+$: m/z = 422.1; Found: 422.3. ^1H NMR (DMSO-d_6, 300 MHz) for TFA salt: δ 8.55 (2H, m), 8.40 (2H, m), 7.48 (1H, m), 7.25–7.22 (3H, m), 7.09 (1H, s), 5.19 (1H, m), 2.64 (3H, d, J = 0.9 Hz), 1.40 (3H, d, J = 6.6 Hz) ppm. ^{19}F NMR (DMSO-d_6, 282 MHz) for TFA salt: δ -74.2, -114.0 ppm.

Example 11. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 2-amino-6-bromopurine (0.01353 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 10, step 2; 0.016 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.01102 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{18}FN_8OS(M+H)^+$: m/z = 437.1; Found: 437.3. ^{1}H NMR (DMSO-d_6, 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.46 (1H, m), 7.20–7.13 (7H, m), 5.18 (1H, m), 2.66 (3H, s), 1.33 (3H, d, J = 6.9 Hz) ppm. ^{19}F NMR (DMSO-d_6, 282 MHz) for TFA salt: δ -74.0, -114.0 ppm.

Example 12. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.318 mmol) and (3,5-difluorophenyl)boronic acid (60.3 mg, 0.382 mmol) in 1,4-

dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO4, and concentrated. The residue was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to provide the desired product (42 mg, 38.0%). LCMS calculated for $C_{15}H_{12}F_2N_5OS(M+H)^+$: m/z = 348.1; Found: 348.2.

Step 2. 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

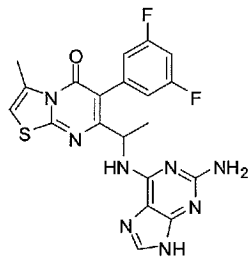
To a stirred solution of 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.042 g, 0.12 mmol) in tetrahydrofuran (0.3 mL) and water (0.0873 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.14 mmol) at room temperature and stirred for 1 hour. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate, and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (36 mg, 92.7%). LCMS calculated for $C_{15}H_{14}F_2N_3OS(M+H)^+$: m/z = 322.1; Found: 322.3.

Step 3. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (0.01258 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.017 g, 0. 053 mmol), and *N,N*-diisopropylethylamine (0.011 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{16}F_2N_7OS(M+H)^+$: m/z = 440.1; Found: 440.3. ^{1}H NMR (DMSO-d_6, 300 MHz) for TFA salt: δ 8.55 (1H, m), 8.39 (2H, m), 7.29 (1H, m), 7.15–7.11 (3H, m), 5.17 (1H, m), 2.64 (3H, d, J = 1.2 Hz), 1.42 (3H, d, J = 6.9 Hz) ppm.

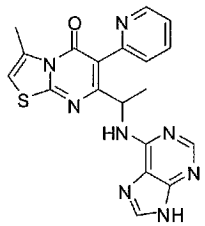
Example 13. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-

5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 2-amino-6-bromopurine (0.01436 g, 0.006712 mmol), 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 12, step 2; 0.018 g, 0. 056 mmol), and *N,N*-diisopropylethylamine (0.01171 mL, 0.006722 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{17}F_2N_8OS(M+H)^+$: m/z = 455.1; Found: 455.3. ^{1}H NMR (DMSO-d_6, 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.26–7.06 (6H, m), 5.16 (1H, m), 2.66 (3H, d, *J* = 1.2 Hz), 1.36 (3H, d, *J* = 6.9 Hz) ppm.

Example 14. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. 7-(1-azidoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 2-(tributylstannyl)pyridine (Aldrich, 0.176 g, 0.382 mmol), 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 3; 0.10 g, 0.318 mmol), and tetrakis(triphenylphosphine)palladium (0) (0.0184 g, 0.0159 mmol) in 1,4-dioxane (0.5 mL) was heated at 65 °C overnight. After being cooled and quenched with saturated ammonium chloride, the resulting mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried and evaporated to dryness. The residue was purified on silica gel, eluting with 0 to 100% EtOAc in hexane, to provide the desired product (13 mg, 13%). LCMS calculated for $C_{14}H_{13}N_6OS(M+H)^+$: m/z = 313.1; Found: 313.0.

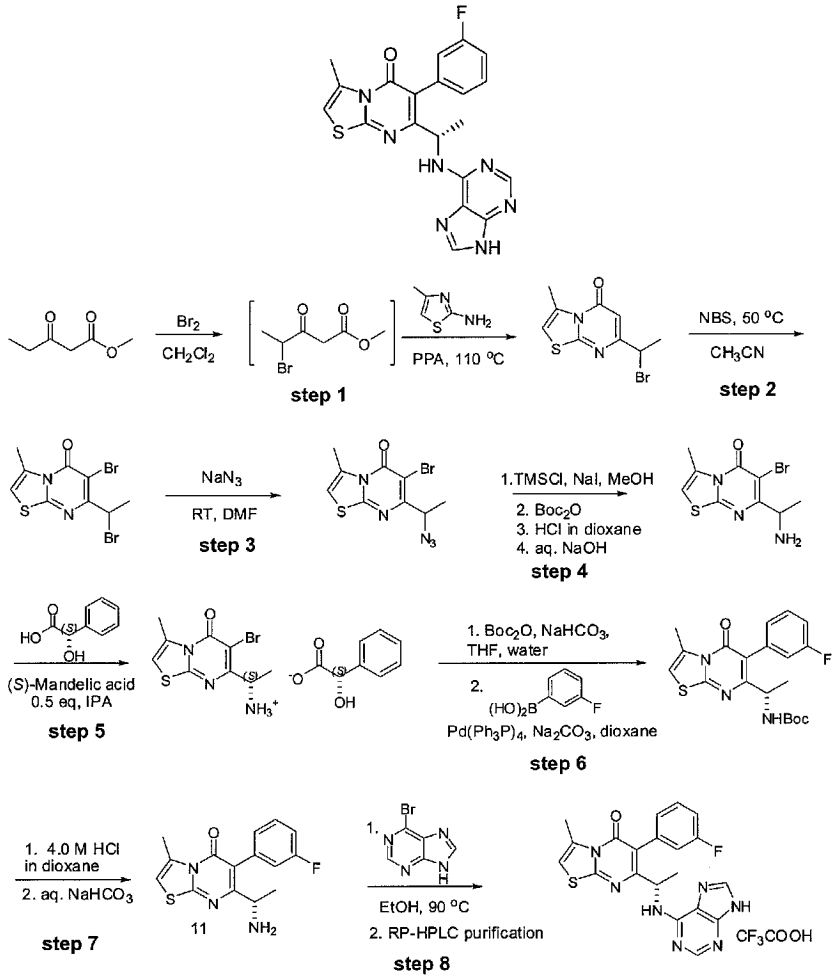
Step 2. 7-(1-aminoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.012 g, 0.039 mmol) in tetrahydrofuran (0.1 mL) and water (0.0285 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.047 mmol) at room temperature and stirred for 1 hour. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step. LCMS calculated for $C_{14}H_{15}N_4OS(M+H)^+$: m/z = 287.1; Found: 287.0.

Step 3. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

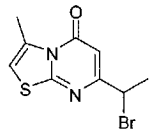
A mixture of 6-bromo-9H-purine (9.300 mg, 0.004673 mmol), 7-(1-aminoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (11 mg, 0.039 mmol), and *N,N*-diisopropylethylamine (8.152 μL, 0.004680 mmol) in ethanol (0.3 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the residue was purified on RP-HPLC (eluting with a gradient of methanol/water containing 1% TFA) to provide the product as a TFA salt. LCMS calculated for $C_{19}H_{17}N_8OS(M+H)^+$: m/z = 405.1; Found: 405.3.

Example 15. (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one



5

Step 1. 7-(1-Bromoethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one

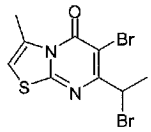


A solution of 3-oxopentanoic acid methyl ester (12.5 g, 96.0 mmol) in methylene chloride (50 mL) was cooled with an ice water bath. The outlet of the flask was attached to a NaOH trap. Bromine (5.19 mL, 101 mmol) in methylene chloride (10 mL, 200 mmol) was added dropwise over a 20-min period, and the reaction mixture was allowed to warm to room temperature and then stirred overnight. The reaction mixture was bubbled with nitrogen for 30 min and then concentrated to give an oil. This oil was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.89 (q, J = 6.9 Hz, 1H), 3.85 (s, 2H), 3.63 (s, 3H), 1.64 (d, J = 6.7 Hz, 3H).

Into a 3-neck flask fitted with a condenser, a thermometer, and a nitrogen inlet was added polyphosphoric acid (50.0 g, 458 mmol). The flask was heated to ~ 70 °C to give a liquid that was easy to stir. 4-Methyl-1,3-thiazol-2-amine (10.0 g, 87.6 mmol) was added in small portions with stirring. The internal temperature slowly increased to 78 °C upon mixing. The crude oil obtained above was then added to the flask *via* a pipette and the mixture was heated to 110 °C under nitrogen. After 6 h of heating, HPLC indicated that the reaction was complete.

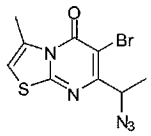
The reaction mixture was cooled to ~ 35 °C. Water (70 mL) and EtOAc (200 mL) were added. The mixture was stirred until all solids dissolved. The organic layer was separated. The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic extracts were washed with 1 N aqueous HCl (40 mL x2) with sat. $NaHCO_3$ (50 mL x 2) and brine (30 mL). The organic layer was dried and concentrated to give 7-(1-bromoethyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one as a yellow solid (11.8 g, 49.3%). LCMS calculated for $C_9H_{10}BrN_2OS$ $(M+H)^+$: m/z 274.96, 272.96; Found: 274.75, 272.75.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (m, 1H), 6.27 (s, 1H), 5.17 (q, J = 6.9 Hz, 1H), 2.65 (s, 3H), 1.85 (d, J = 6.9 Hz, 3H).

Step 2. 6-Bromo-7-(1-bromoethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one



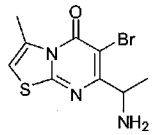
Under nitrogen, a suspension of 7-(1-bromoethyl)-3-methyl-5*H*-[1,3]thiazolo[3,2-a]pyrimidin-5-one(13.2 g, 48.3 mmol) in acetonitrile (100 mL, 2000 mmol) was stirred until a clear solution was obtained. *N*-Bromosuccinimide (9.891 g, 55.57 mmol) was then added and the reaction mixture was stirred at 50 °C. After 20 min, HPLC indicated that the reaction was complete. A solution of sodium sulfite (3.046 g, 24.16 mmol) in water (50 mL) was added and the mixture was stirred at room temperature for 20 min. Water (200 mL) was added slowly and the mixture stirred at room temperature for 30 min. and then filtered. The solid was washed with water (100 mL x 3) and dried to give 6-bromo-7-(1-bromoethyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one as an off-white solid (15.61 g, 91%). LCMS calculated for $C_9H_9Br_2N_2OS$ $(M+H)^+$: m/z 352.87, 354.87; Found: 352.65, 354.60. ^1H NMR (400 MHz, DMSO-d_6) δ 7.15 (q, J = 1.3 Hz, 1H), 5.51 (q, J = 6.7 Hz, 1H), 2.66 (d, J = 1.2 Hz, 3H), 1.90 (d, J = 6.7 Hz, 3H).

Step 3. 7-(1-Azidoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one



To a suspension of 6-bromo-7-(1-bromoethyl)-3-methyl-5*H*-[1,3]thiazolo[3,2-a]pyrimidin-5-one (6.85 g, 19.4 mmol) in *N,N*-dimethylformamide (30.1 mL) was added sodium azide (1.45 g, 22.4 mmol). The mixture slowly turned clear after 5-10 min. After 50 min, a solution of sodium bicarbonate (4.7 g, 56 mmol) in water (90 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 1 h and the solid precipitates were filtered off. The solid was then washed with water (30 mL x 3), and dried to give 7-(1-azidoethyl)-6-bromo-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one as an off-white solid (5.94 g, 97.2%). LCMS calculated for $C_9H_9BrN_5OS$ $(M+H)^+$: m/z 313.96, 315.96; Found: 313.75, 315.75. ^1H NMR (400 MHz, DMSO-d_6) δ 7.15 (q, J = 1.3 Hz, 1H), 4.83 (q, J = 6.8 Hz, 1H), 2.67 (d, J = 1.4 Hz, 3H), 1.48 (d, J = 6.8 Hz, 3H).

Step 4. 7-(1-Aminoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one

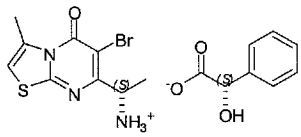


7-(1-Azidoethyl)-6-bromo-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (22.6 g, 71.9 mmol) was mixed with methanol (200 mL). Sodium iodide (64.7 g, 432 mmol) was added and stirred at room temperature for 10 min. Chlorotrimethylsilane (54.8 mL, 432 mmol) was dissolved in methanol (29.1 mL) and added dropwise over 10 min. at 5-25 °C. The reaction mixture was stirred at room temperature for 10 min. HPLC and TLC showed that the reaction was complete. The reaction was quenched by addition of a solution of sodium thiosulfate (69.4 g, 439 mmol) in water (259 ml) while maintaining the batch temperature at 5- 25 °C. A large amount of solid was formed, and the pH of the mixture was 3. The mixture was stirred at 0- 5 °C for 30 min. The pH was adjusted to 11 using 3 N aqueous sodium hydroxide (85 mL).
In order to facilitate product purification and isolation, the *N*-Boc derivative of the product was prepared. To the mixture was added di-*t*-butyldicarbonate (28.3 g, 129 mmol) and the reaction mixture was stirred at room temperature for 2 h. HPLC indicated a small amount of amine remained unreacted. Additional di-*t*-butyldicarbonate (10.0 g, 45.8 mmol) was added followed by 3 N aqueous sodium hydroxide (15 mL) to adjust the pH to 11. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with ethyl acetate (150 mL x 3). The organic solution which contained the *N*-Boc derivative of the product was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was added to a 4 M solution of hydrogen chloride in 1,4-dioxane (206 mL, 824 mmol) and stirred at room temperature for 1.5 h. HPLC indicated the *N*-Boc-deprotection was complete. The hydrochloride salt of the product was isolated by filtration, the solid washed with MTBE, dried by suction filtration for 1 h to give 7-(1-aminoethyl)-6-bromo-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one hydrochloride salt (25.1 g) as a purple powder.

The hydrochloride salt was dissolved in water (50 mL) and a 50% solution of sodium hydroxide (about 5 mL) was added to adjust the pH to 11. The mixture was stirred at room temperature for 20 min. The product precipitated and was isolated by filtration. The wet solid

was washed with water (10 mL) and dried on the filter under vacuum for 18 h to give 7-(1-aminoethyl)-6-bromo-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (18.8 g, 65.2 mmol, 90.7 % yield) as a yellow powder. LCMS calculated for $C_9H_{11}BrN_3OS$ $(M+H)^+$: m/z 287.97, 289.97; Found: 287.75, 289.75. ^1H NMR (400 MHz, DMSO-d_6) 7.08 (q, J = 1.3 Hz, 1H), 4.19 (q, J = 6.7 Hz, 1H), 2.65 (d, J = 1.3 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H).

Step 5. (S)-1-(6-bromo-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethanaminium (S)-2-hydroxy-2-phenylacetate



7-(1-Aminoethyl)-6-bromo-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (18.8 g, 65.2 mmol) was dissolved in isopropanol (375 mL) at reflux and then (*S*)-(+)-mandelic acid (4.84 g, 31.8 mmol) in isopropanol (375 mL) was added dropwise to the amine solution over 35 min. The reaction mixture was allowed to cool to about 72 °C and solid precipitation was observed. The slurry was cooled to room temperature and stirred for 1 hour. The solid product was collected by filtration. The wet cake was washed with isopropanol (100 mL) and dried on the filter under suction for 1 h to give the product (*S*)-1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate (11.9 g) as a white solid. Chiral HPLC analysis was performed on a Lux Cellulose-2, 4.6 x 250 mm, 5 micron column using 60% ethanol/40% hexanes as the mobile phase at a flow rate of 1 mL/ min. The major enantiomer eluted at retention time 11.21 min (99.0 area %). The minor enantiomer eluted at retention time 14.31 min (0.96 area %). The e.e. of the desired product was 98.08%.

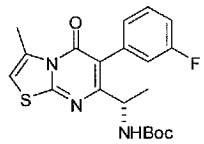
The product at 98.08% e.e. (11.9 g) was suspended in isopropanol (750 mL) and heated under reflux for 30 min. The slurry was cooled to room temperature with stirring. The solid was collected by filtration. The wet solid was washed with isopropanol (100 mL) and dried on the filter under suction for 18 h to give 10.9 g of white solid. Chiral HPLC by the method described above gave e.e. of 98.48%.

The product at 98.48% e.e. (10.9 g) was stirred in a solution of sodium carbonate (3.9 g, 37 mmol) in water (100 mL) at room temperature for 30 min. The solid free base was collected

by filtration, washed with water (20 mL) and dried on the filter under suction for 2 h to give a slightly wet cake (13 g). The wet solid was dissolved in isopropanol (325 mL) at reflux and a solution of (*S*)-(+)-mandelic acid (3.613 g, 23.75 mmol) in isopropanol (325 mL) was added dropwise over 20 min to the free base solution. The solution was cooled to room temperature with stirring. The solid product was collected by filtration, washed with isopropanol (100 mL) and dried on the filter under suction for 48 h to give pure product (*S*)-1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate (8.4 g, 19.08 mmol, 29.3 % yield) as a white solid. The e.e. of this sample was determined to be 100 % as no minor enantiomer (retention time = 14.31 min) was detected. LCMS calculated for $C_9H_{11}BrN_3OS$ $(M+H)^+$ for the free base: m/z 289.97, 287.97; Found: 289.75, 287.75. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 7.5 Hz, 2H), 7.22 (dd, J = 7.1, 7.5 Hz, 2H), 7.16 (m, 2H), 4.61 (s, 1H), 4.47 (q, J = 6.9 Hz, 1H), 2.68 (d, J = 1.1 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H).

In order to determine the absolute stereochemistry of the product, a sample was sublimed at about 105 °C to provide colorless needles suitable for X-ray crystal structure analysis. The study determined the absolute configuration of the amine bearing carbon (C-8) is *S* (see Example 16 and Figure 1).

Step 6. (S)-tert-Butyl 1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethylcarbamate

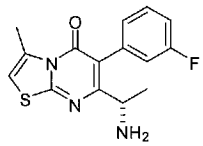


(*S*)-1-(6-Bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate (4.93 g, 11.2 mmol) was dissolved in THF (100 mL) and water (33 mL). Di-*t*-butyldicarbonate (3.03 g, 13.9 mmol) was added, followed by sodium bicarbonate (1.88 g, 22.4 mmol). The reaction mixture was stirred at room temperature for 30 min. at which point the HPLC showed the reaction was near complete. Additional di-*t*-butyldicarbonate (0.49 g, 2.24 mmol) was then added and the reaction mixture was stirred at room temperature for 1 hour. The reaction was shown to be complete by HPLC. The reaction mixture was diluted with

water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The ethyl acetate solution was concentrated to give (*S*)-*tert*-butyl 1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)ethylcarbamate (5.46 g, 14.1 mmol, 126% yield) which was used in the subsequent Suzuki coupling reaction without further purification.

(*S*)-*tert*-Butyl 1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)ethylcarbamate (5.46 g, 14.1 mmol) and (3-fluorophenyl)boronic acid (2.95 g, 21.1 mmol) were suspected in 1,4-dioxane (110 mL). A solution of sodium carbonate (4.47g, 42.2 mmol) in water (27 mL) was added to the mixture followed by tetrakis(triphenylphosphine)palladium(0) catalyst (0.81 g, 0.70 mmol). The reaction mixture was degassed and heated under nitrogen at 100 °C for 16 h. HPLC indicated the starting material was consumed. The reaction mixture was cooled to room temperature and water (100 mL) was added. The resultant mixture was extracted with ethyl acetate (2 x 100 mL). The ethyl acetate solution was washed with saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel using 1- 50% ethyl acetate in hexane as eluent to give (*S*)-*tert*-butyl 1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)ethylcarbamate (4.34 g, 10.8 mmol, 76%) as an off-white solid. LCMS calculated for $C_{20}H_{23}FN_3O_3S$ $(M+H)^+$: m/z 404.1; Found 404.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.48 (ddd, *J* = 8.1, 7.8, 6.2 Hz, 1H), 7.18 (m, 3H), 7.05 (q, *J* = 1.3 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 4.41 (m, 1H), 2.66 (d, *J* = 1.3 Hz, 3H), 1.33 (s, 9H), 1.13 (d, *J* = 6.8 Hz, 3H).

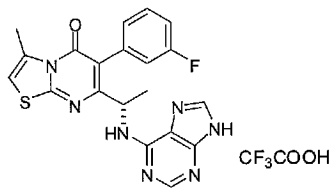
Step 7. (S)-7-(1-Aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one



(*S*)-*tert*-Butyl 1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)ethylcarbamate (4.15 g, 10.3 mmol) was dissolved in a 4.0 M solution of hydrogen chloride in 1,4-dioxane (25.7 mL, 102.8 mmol) and the solution was stirred at room temperature for 45 min. HPLC indicated that the reaction was complete. To the solution was added water (10 mL) followed by 3 N aqueous sodium hydroxide solution at 0- 5 °C to adjust the pH to 10. The

aqueous mixture was extracted with ethyl acetate (2 x 30 mL). The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (*S*)-7-(1-Aminoethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (3.30 g, 10.88 mmol, 103% yield). LCMS calculated for $C_{15}H_{15}FN_3OS$ $(M+H)^+$: m/z 304.08; Found 303.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (ddd, J = 8.1, 7.9, 5.9 Hz, 1H), 7.19 (m, 1H), 7.12 (m, 2H) 7.04 (q, J = 1.1 Hz, 1H), 3.57 (q, J = 6.6 Hz, 1H), 2.64 (d, J = 1.3 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H)

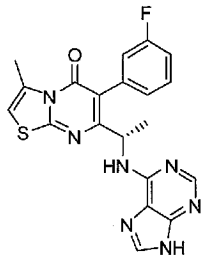
Step 8. (S)-7-(1-(9H-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



(*S*)-7-(1-Aminoethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (2.30 g, 7.58 mmol), 6-bromo-9*H*-purine (2.716 g, 13.65 mmol), *N,N*-diisopropylethylamine (6.60 mL, 37.9 mmol) were dissolved in ethanol (15 mL) and the resultant mixture was heated at reflux under a nitrogen atmosphere for 17 h. HPLC indicated the reaction was complete. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel using gradient elution starting at 100% DCM with increasing polarity to 25% of a mixture of DCM/MeOH/ aq.NH_4OH (100:5:0.5, v/v/v) in DCM. After the silica chromatography, 2.1 g of crude product was obtained. This crude product was further purified by preparative reversed phase HPLC using 0.1% TFA in water and acetonitrile as mobile phases at a flow rate of 60 mL/min. on a SunFire C18, 5 μM, 30 x 100 mm column. Pure (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt (trifluoroacetic acid salt) (1.86 g, 3.47 mmol, 45.8 % yield) was obtained as a white solid after lyophilization. LCMS calculated for $C_{20}H_{17}FN_7OS$ $(M+H)^+$ for the free base: m/z 422.1; Found: 422.0).^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (br s, 1H), 8.53 (s, 1H), 8.51 (s, 1H), 7.47 (m, 1H), 7.21 (m, 3H), 7.09 (s, 1H), 5.23 (m, 1H), 2.65 (d, J = 1.3 Hz, 3H), 1.43 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ

164.0, 162.1 (J_{CF} = 244.9 Hz), 160.5, 160.3, 150.9, 147.6, 147.5, 144.4, 135.9, 135.9, 130.2 (J_{CF} = 8.3 Hz), 126.9, 117.4 (J_{CF} = 22.6 Hz), 116.1, 114.8 (J_{CF} = 21.5 Hz), 111.1, 107.8, 48.5, 19.6, 18.0. Reversed phase analytical HPLC showed purity at 99.8 area %. Chiral HPLC analysis was performed on Chiralcel OJ-H, 4.6 x 250 mm, 5 micron column using 60 % ethanol/40 % hexanes as eluent at a flow rate of 0.5 mL/min. The peak for the desired enantiomer (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one was observed at a retention time of 21.171 min. (99.1 area %). The minor peak for the undesired enantiomer (*R*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one was observed at a retention time of 13.358 min (0.9 area %). The enantiomeric excess of the desired enantiomer was 98.2%.

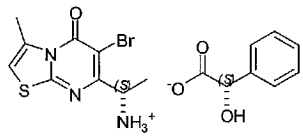
Example 15A. (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one



A mixture of (*S*)-7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (108.2 g, 357 mmol), 6-chloropurine (71.73 g, 464.1 mmol), and *N*,*N*-diisopropylethylamine (74.6 mL, 428.4 mmol) in 1-butanol (952 mL) was degassed with nitrogen bubbling for 5 minutes. The reaction mixture was heated at 105 °C under nitrogen for 15 hours, at which point HPLC indicated amine was consumed. The reaction mixture was cooled down to room temperature before being treated with water (200 mL) at room temperature. The resulting mixture was concentrated under reduced pressure to give an oily residue and the residue was treated with CH_2Cl_2 (1000 mL) to give a brownish clear solution. The resulting solution was washed with 2.5% aqueous sodium carbonate solution (Na_2CO_3, 250 mL x 2) and the organic layer was concentrated under reduced pressure to afford the crude desired product as a brownish solid. The solution of the crude desired product in CH_2Cl_2 was absorbed onto silica gel (300 g)

and the dried silica gel was loaded onto a flash column. The flash column was eluted with pure CH_2Cl_2 and a mixture of CH_2Cl_2, MeOH and aqueous NH_4OH (2000:10:5) to afford pure desired product. The fractions containing pure desired product were combined and concentrated under reduced pressure. The resulting yellowish solid (90.3 g) was dissolved in a mixture of CH_2Cl_2 and methanol (500 : 50 mL). The resulting solution was treated with ethyl acetate (900 mL) and the resulting mixture was distilled until the internal solution temperature reached 68 °C. The mixture was then cooled to room temperature and subsequently to 0 - 5 °C for 1 hour. The solids were collected by filtration, washed with cold ethyl acetate (100 mL), and dried overnight on the filter under vacuum to afford (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (89.5 g, 59.4% yield, 99.4% ee) as a light yellowish solid. LCMS calculated for $C_{20}H_{17}FN_7OS$ $(M+H)^+$ for the free base: m/z 422.1; Found: 422.0; ^1H NMR (500 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.99 (br s, 1H), 7.45 (m, 1H), 7.21-7.12 (m, 3H), 6.8 (m, 1 H), 6.42 (s, 1H), 5.52 (br s, 1H), 2.79 (d, J = 1.3 Hz, 3H), 1.43 (d, J = 7.0 Hz, 3H).

Example 16. X-Ray Crystallography of (S)-1-(6-bromo-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethanaminium (S)-2-hydroxy-2-phenylacetate (From Example 15, Step 5)



In order to determine the absolute stereochemistry of the product from Example 15, step 5, a sample was sublimed at about 105 °C to provide colorless needles suitable for X-ray crystal structure analysis. The study determined the absolute configuration of the amine bearing carbon (C-8) is *S*.

DATA COLLECTION: Bruker SMART APEX-II CCD system, MoKalpha radiation, standard focus tube , anode power = 50kV x 42 mA, crystal to plate distance = 5.0 cm, 512 x 512 pixels/frame, beam center = (256.13,253.14), total frames = 1081, oscillation/frame = 0.50°, exposure/frame = 300.1 sec/frame, SAINT integration, hkl min/max = (-4, 7, -14, 14, -31, 35), data input to shelx = 11285 , unique data = 3870 , two-theta range = 3.82 to 53.64°, completeness to two-theta 53.64 = 99.70%, R(int-xl) = 0.0908, SADABS correction applied.

SOLUTION AND REFINEMENT: Structure solved using XS(Shelxtl), refined using shelxtl software package, refinement by full-matrix least squares on F^2, scattering factors from Int. Tab. Vol C Tables 4.2.6.8 and 6.1.1.4, number of data = 3870 , number of restraints = 0 , number of parameters = 309 , data/parameter ratio = 12.52, goodness-of-fit on F^2 = 0.99, R indices[I>4sigma(I)] R1 = 0.0455, wR2 = 0.0674, R indices(all data) R1 = 0.1059, wR2 = 0.0825, max difference peak and hole = 0.420 and -0.863 e/Å^3, refined flack parameter = 0.025(11). All of the hydrogen atoms have been found from a difference map and fully refined.

CRYSTAL DATA: C17 H18 Br N3 O4 S, from sublimation @ 105 °C, colorless, needle, ~0.160 x 0.020 x 0.020 mm, orthorhombic, P212121, a = 5.5572(18) Å, b = 11.547(4) Å, c = 28.207(10) Å, Vol = 1810.1(11) Å^3, Z = 4 , T = -100.°C, Formula weight = 440.31, Density = 1.616 g/cm^3, μ(Mo) = 2.41 mm^{-1}.

RESULTS: This study determined the structure of C17,H18,N3,O4,S1,Br1 for the product of Example 15, step 5. The asymmetric unit contains one of each molecule as shown in Figure 1 with thermal ellipsoids drawn to the 50% probability level. The predicted structure was confirmed. The molecules form an infinite hydrogen bonded chain via the NH3's along the a-axis which is the needle axis, as shown in Figure 2. The absolute configuration was determined to be *S* at both C8 and C16 based upon the refinement of the flack parameter = 0.02(5). The configuration of C16 was known to be *S*.

Table A1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	5816(1)	1172(1)	1875(1)	34(1)
S(1)	-2800(2)	-1679(1)	1030(1)	28(1)
O(1)	2992(7)	-875(4)	2278(1)	48(1)
O(2)	-1818(7)	-1946(3)	-193(1)	33(1)
O(3)	-1693(5)	1147(3)	-24(1)	27(1)
O(4)	-4576(7)	-176(3)	77(1)	32(1)
N(1)	285(6)	-1133(4)	1670(1)	22(1)
N(2)	444(8)	26(3)	965(2)	25(1)
N(3)	2679(10)	1576(4)	395(2)	23(1)
C(1)	2242(9)	648(4)	1173(2)	20(1)
C(2)	3198(8)	351(4)	1606(2)	22(1)
C(3)	2267(10)	-571(4)	1891(2)	29(1)
C(4)	-474(9)	-820(4)	1219(2)	20(1)
C(5)	-1135(9)	-2023(4)	1878(2)	25(1)

	C(6)	-2805(11)	-2394(5)	1565(2)	26(1)
	C(7)	-807(18)	-2456(6)	2365(2)	41(2)
	C(8)	2920(10)	1736(4)	917(2)	23(1)
	C(9)	1254(13)	2703(5)	1078(3)	32(2)
	C(10)	-755(11)	-530(4)	-802(2)	21(1)
	C(11)	-2631(10)	-858(4)	-1102(2)	26(1)
	C(12)	-2597(11)	-528(5)	-1570(2)	28(1)
	C(13)	-732(12)	127(4)	-1755(2)	31(1)
	C(14)	1149(11)	434(5)	-1457(2)	31(1)
	C(15)	1156(10)	102(4)	-981(2)	26(1)
	C(16)	-926(12)	-817(4)	-274(2)	24(1)
	C(17)	-2506(10)	130(4)	-50(2)	23(1)

Table A2. Bond lengths [Å] and angles (deg)

Br(1)-C(2)	1.896(5)
S(1)-C(4)	1.714(5)
S(1)-C(6)	1.719(6)
O(1)-C(3)	1.215(6)
O(2)-C(16)	1.413(6)
O(3)-C(17)	1.260(6)
O(4)-C(17)	1.256(6)
N(1)-C(4)	1.387(6)
N(1)-C(3)	1.422(6)
N(1)-C(5)	1.423(6)
N(2)-C(4)	1.314(6)
N(2)-C(1)	1.362(6)
N(3)-C(8)	1.489(6)
C(1)-C(2)	1.375(7)
C(1)-C(8)	1.497(7)
C(2)-C(3)	1.431(7)
C(5)-C(6)	1.350(8)
C(5)-C(7)	1.474(8)
C(8)-C(9)	1.521(8)
C(10)-C(15)	1.385(8)
C(10)-C(11)	1.395(7)
C(10)-C(16)	1.529(7)
C(11)-C(12)	1.375(7)
C(12)-C(13)	1.385(8)
C(13)-C(14)	1.388(8)
C(14)-C(15)	1.394(8)
C(16)-C(17)	1.538(7)
C(4)-S(1)-C(6)	90.4(3)
C(4)-N(1)-C(3)	121.2(4)
C(4)-N(1)-C(5)	113.4(4)
C(3)-N(1)-C(5)	125.4(4)

C(4)-N(2)-C(1)	116.3(5)
N(2)-C(1)-C(2)	122.2(5)
N(2)-C(1)-C(8)	114.8(5)
C(2)-C(1)-C(8)	122.7(5)
C(1)-C(2)-C(3)	123.0(5)
C(1)-C(2)-Br(1)	121.9(4)
C(3)-C(2)-Br(1)	115.1(4)
O(1)-C(3)-N(1)	121.2(5)
O(1)-C(3)-C(2)	126.8(5)
N(1)-C(3)-C(2)	111.9(5)
N(2)-C(4)-N(1)	125.1(5)
N(2)-C(4)-S(1)	123.6(4)
N(1)-C(4)-S(1)	111.3(3)
C(6)-C(5)-N(1)	110.0(5)
C(6)-C(5)-C(7)	125.9(5)
N(1)-C(5)-C(7)	124.1(5)
C(5)-C(6)-S(1)	114.8(5)
N(3)-C(8)-C(1)	110.5(4)
N(3)-C(8)-C(9)	109.4(5)
C(1)-C(8)-C(9)	108.6(4)
C(15)-C(10)-C(11)	119.6(5)
C(15)-C(10)-C(16)	121.2(5)
C(11)-C(10)-C(16)	119.1(5)
C(12)-C(11)-C(10)	119.8(5)
C(11)-C(12)-C(13)	121.5(6)
C(12)-C(13)-C(14)	118.4(5)
C(13)-C(14)-C(15)	121.0(5)
C(10)-C(15)-C(14)	119.6(5)
O(2)-C(16)-C(10)	112.3(4)
O(2)-C(16)-C(17)	113.0(5)
C(10)-C(16)-C(17)	106.3(4)
O(4)-C(17)-O(3)	125.1(5)
O(4)-C(17)-C(16)	116.1(5)
O(3)-C(17)-C(16)	118.8(5)

Table A3. Anisotropic displacement parameters (A^2 x 10^3) (symmetry transformations used to generate equivalent atoms. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12)

	U11	U22	U33	U23	U13	U12
Br(1)	27(1)	40(1)	36(1)	-4(1)	-6(1)	-9(1)
S(1)	27(1)	24(1)	33(1)	2(1)	-5(1)	-7(1)
O(1)	54(3)	56(3)	33(3)	9(2)	-21(2)	-11(2)
O(2)	41(3)	13(2)	46(3)	3(2)	6(2)	4(2)
O(3)	33(2)	14(2)	35(2)	5(2)	-7(1)	0(2)

	O(4)	31(3)	21(2)	44(3)	-1(2)	8(2)	0(2)
	N(1)	22(2)	22(2)	21(2)	1(2)	-3(2)	-3(2)
	N(2)	26(3)	21(2)	26(3)	5(2)	-2(2)	0(2)
	N(3)	27(3)	22(3)	19(3)	4(2)	3(2)	-8(2)
	C(1)	16(3)	19(3)	26(3)	-4(2)	0(2)	-3(2)
	C(2)	13(3)	23(3)	29(3)	1(3)	1(2)	-2(2)
	C(3)	29(3)	31(3)	27(3)	-1(3)	-5(3)	2(3)
	C(4)	23(3)	17(3)	20(3)	4(2)	0(2)	1(2)
	C(5)	26(3)	22(3)	29(3)	11(3)	6(3)	-2(2)
	C(6)	22(3)	17(3)	40(4)	4(3)	0(3)	-4(3)
	C(7)	56(5)	36(4)	31(4)	11(3)	1(4)	-2(4)
	C(8)	23(3)	21(3)	26(3)	-7(3)	-4(2)	-4(2)
	C(9)	34(5)	21(3)	41(5)	-3(3)	6(3)	-9(3)
	C(10)	23(3)	17(3)	23(3)	1(2)	6(3)	9(3)
	C(11)	26(3)	22(3)	31(4)	1(3)	3(3)	-6(3)
	C(12)	26(3)	19(3)	38(4)	-7(3)	-4(3)	11(3)
	C(13)	37(3)	22(3)	32(4)	3(2)	5(3)	8(3)
	C(14)	22(4)	25(3)	45(4)	8(3)	10(3)	0(3)
	C(15)	27(3)	20(3)	33(3)	-1(3)	7(3)	6(3)
	C(16)	30(3)	10(3)	31(3)	-2(2)	1(3)	3(3)
	C(17)	29(3)	18(3)	22(3)	1(2)	-3(3)	6(3)

Table A4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3)

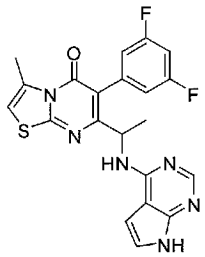
	x	y	z	U(eq)
H(2)	-3600(200)	-1860(80)	-110(30)	160(40)
H(3)	4250(110)	910(50)	254(19)	59(17)
H(3A)	1260(150)	1240(60)	310(20)	80(20)
H(3B)	2910(100)	2160(50)	266(19)	27(18)
H(6)	-3610(100)	-2890(40)	1579(18)	25(18)
H(7)	-2240(160)	-3020(80)	2480(30)	120(30)
H(7A)	-1360(90)	-1900(50)	2583(17)	30(17)
H(7B)	640(120)	-2750(50)	2426(19)	41(19)
H(8)	4800(80)	1970(40)	1003(17)	28(15)
H(9)	2070(100)	3440(50)	950(20)	56(19)
H(9A)	1570(110)	2790(50)	1430(20)	60(20)
H(9B)	-210(100)	2520(50)	1035(19)	34(19)
H(11)	-3890(80)	-1350(40)	-963(14)	16(12)
H(12)	-3720(100)	-740(50)	-1780(20)	60(20)
H(13)	-670(100)	380(40)	-2129(18)	40(15)
H(14)	2390(110)	910(50)	-1573(18)	45(17)
H(15)	2710(120)	320(50)	-760(20)	70(20)
H(16)	780(100)	840(40)	-125(18)	50(16)

Table A5. Torsion angles [deg].

C(4)-N(2)-C(1)-C(2)	5.5(7)
C(4)-N(2)-C(1)-C(8)	-168.8(4)
N(2)-C(1)-C(2)-C(3)	-5.2(8)
C(8)-C(1)-C(2)-C(3)	168.7(5)
N(2)-C(1)-C(2)-Br(1)	176.5(4)
C(8)-C(1)-C(2)-Br(1)	-9.6(7)
C(4)-N(1)-C(3)-O(1)	-177.1(5)
C(5)-N(1)-C(3)-O(1)	4.4(8)
C(4)-N(1)-C(3)-C(2)	3.3(7)
C(5)-N(1)-C(3)-C(2)	-175.2(4)
C(1)-C(2)-C(3)-O(1)	-179.0(5)
Br(1)-C(2)-C(3)-O(1)	-0.7(8)
C(1)-C(2)-C(3)-N(1)	0.6(7)
Br(1)-C(2)-C(3)-N(1)	179.0(3)
C(1)-N(2)-C(4)-N(1)	-1.5(7)
C(1)-N(2)-C(4)-S(1)	178.2(4)
C(3)-N(1)-C(4)-N(2)	-3.0(7)
C(5)-N(1)-C(4)-N(2)	175.6(5)
C(3)-N(1)-C(4)-S(1)	177.2(4)
C(5)-N(1)-C(4)-S(1)	-4.1(5)
C(6)-S(1)-C(4)-N(2)	-177.2(5)
C(6)-S(1)-C(4)-N(1)	2.5(4)
C(4)-N(1)-C(5)-C(6)	3.8(6)
C(3)-N(1)-C(5)-C(6)	-177.6(5)
C(4)-N(1)-C(5)-C(7)	-175.8(6)
C(3)-N(1)-C(5)-C(7)	2.8(8)
N(1)-C(5)-C(6)-S(1)	-1.8(6)
C(7)-C(5)-C(6)-S(1)	177.7(5)
C(4)-S(1)-C(6)-C(5)	-0.4(5)
N(2)-C(1)-C(8)-N(3)	-34.3(6)
C(2)-C(1)-C(8)-N(3)	151.4(5)
N(2)-C(1)-C(8)-C(9)	85.7(6)
C(2)-C(1)-C(8)-C(9)	-88.6(6)
C(15)-C(10)-C(11)-C(12)	-1.5(8)
C(16)-C(10)-C(11)-C(12)	174.9(5)
C(10)-C(11)-C(12)-C(13)	0.0(8)
C(11)-C(12)-C(13)-C(14)	1.0(8)
C(12)-C(13)-C(14)-C(15)	-0.6(8)
C(11)-C(10)-C(15)-C(14)	1.9(8)

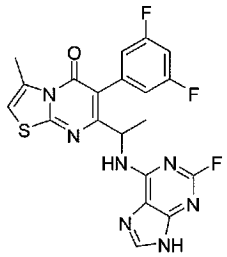
	C(16)-C(10)-C(15)-C(14)	-174.4(5)
	C(13)-C(14)-C(15)-C(10)	-0.9(8)
	C(15)-C(10)-C(16)-O(2)	-141.3(5)
	C(11)-C(10)-C(16)-O(2)	42.3(7)
5	C(15)-C(10)-C(16)-C(17)	94.7(6)
	C(11)-C(10)-C(16)-C(17)	-81.7(6)
	O(2)-C(16)-C(17)-O(4)	-15.1(7)
	C(10)-C(16)-C(17)-O(4)	108.4(5)
	O(2)-C(16)-C(17)-O(3)	167.6(4)
10	C(10)-C(16)-C(17)-O(3)	-68.9(6)

Example 17. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



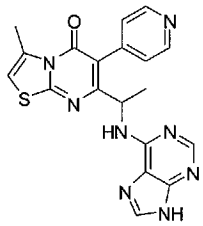
15 A mixture of 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one hydrochloride (0.030 g, 0.084 mmol), 4-chloropyrrolo[2,3-d]pyrimidine (0.013 g, 0.084 mmol), and *N,N*-diisopropylethylamine (0.044 mL, 0.25 mmol) in isopropyl alcohol (0.2 mL) was heated at 100 °C, in a sealed tube, for three days. The resultant mixture was applied on RP-HPLC (XBridge C18 Column, eluting with a gradient of acetonitrile/water 20 containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{21}H_{17}F_2N_6OS(M+H)^+$: m/z = 439.1; Found: 439.1.

Example 18. 6-(3,5-difluorophenyl)-7-{1-[(2-fluoro-9H-purin-6-yl)amino]ethyl}-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

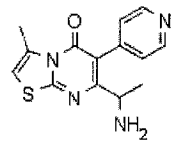


A mixture of 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one hydrochloride (0.030 g, 0.084 mmol), 2-fluoro-6-chloropurine (0.015 g, 0.084 mmol), and *N,N*-diisopropylethylamine (0.044 mL, 0.25 mmol) in isopropyl alcohol (0.2 mL) was heated at 100 °C for three days, in a sealed tube. The resultant mixture was purified on RP-HPLC (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{20}H_{15}F_3N_7OS(M+H)^+$: m/z = 458.1; Found: 458.0.

Example 19. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-4-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



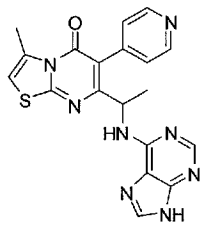
Step 1. 7-(1-aminoethyl)-3-methyl-6-pyridin-4-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-pyridin-4-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.050 g, 0.16 mmol) in tetrahydrofuran (0.5 mL) and water (0.12 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.19 mL, 0.19 mmol) at room

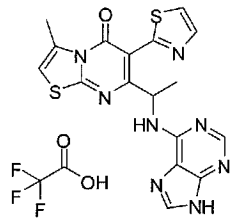
temperature and the mixture was stirred at room temperature for 1 hour. To the mixture was added ethyl acetate (EtOAc) and the mixture was extracted with 1 N HCl two times. The combined extracts were neutralized with solid sodium bicarbonate, and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue, shown two peaks with same desired mass, was used directly in next step. LCMS calculated for $C_{14}H_{15}N_4OS(M+H)^+$: m/z = 287.1; Found: 287.0.

Step 2. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-4-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

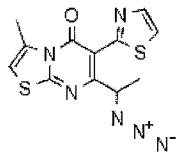


A mixture of 6-bromo-9H-purine (0.064 g, 0.32 mmol), 7-(1-aminoethyl)-3-methyl-6-pyridin-4-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.046 g, 0.16 mmol), and *N,N*-diisopropylethylamine (0.056 mL, 0.32 mmol) in ethanol (0.5 mL) was heated at reflux under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the product as the free base. LCMS calculated for $C_{19}H_{17}N_8OS(M+H)^+$: m/z = 405.1; Found: 405.1.

Example 20. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-(1,3-thiazol-2-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

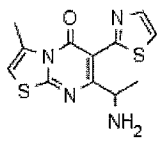


Step 1. 7-(1-azidoethyl)-3-methyl-6-(1,3-thiazol-2-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.32 mmol), and 2-(tributylstannyl)-1,3-thiazole (143 mg, 0.382 mmol) in 1,4-dioxane (3 mL) was added tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.016 mmol). The reaction mixture was heated at 120 °C overnight. After cooling to room temperature, the mixture concentrated under reduced pressure. The crude mixture was purified on silica gel, eluting with 0 to 60% ethyl acetate in hexane, to give the desired product (73 mg, 72%). LCMS calculated for $C_{12}H_{11}N_6OS_2(M+H)^+$: m/z = 319.0; Found: 319.0.

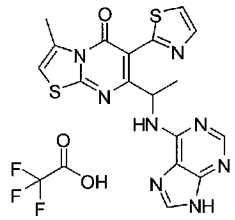
Step 2. 7-(1-aminoethyl)-3-methyl-6-(1,3-thiazol-2-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-(1,3-thiazol-2-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.030 g, 0.094 mmol) in tetrahydrofuran (0.3 mL) and water (0.068 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.11 mL, 0.11 mmol) at room temperature and the mixture was stirred at room temperature for 1 hour. To the mixture was added ethyl acetate and the mixture was extracted with 1 N HCl two times. The combined extracts were neutralized with solid sodium bicarbonate, and extracted with

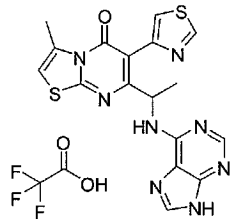
dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step. LCMS calculated for $C_{12}H_{13}N_4OS_2(M+H)^+$: m/z = 293.1; Found: 293.0.

Step 3. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-(1,3-thiazol-2-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

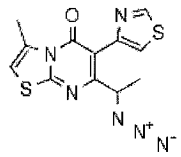


A mixture of 6-bromo-9H-purine (0.038 g, 0.19 mmol), 7-(1-aminoethyl)-3-methyl-6-(1,3-thiazol-2-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.028 g, 0.096 mmol), and *N,N*-diisopropylethylamine (0.033 mL, 0.19 mmol) in ethanol (0.3 mL) was heated at reflux under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% trifluoroacetic acid (TFA)) to give the product as a TFA salt. LCMS calculated for $C_{17}H_{15}N_8OS_2(M+H)^+$: m/z = 411.1; Found: 411.0.

Example 21. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-(1,3-thiazol-4-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

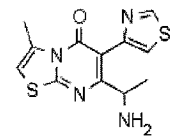


Step 1. 7-(1-azidoethyl)-3-methyl-6-(1,3-thiazol-4-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



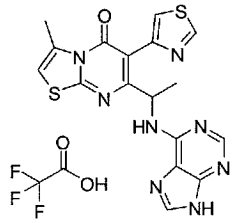
To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.32 mmol) and 4-(tributylstannyl)-1,3-thiazole (143 mg, 0.382 mmol) in 1,4-dioxane (3 mL) was added tetrakis(triphenylphosphine)palladium(0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 120 °C overnight. After cooling to room temperature, the mixture concentrated under reduced pressure. The crude mixture was purified on silica gel, eluting with 0 to 60% EtOAc in hexane, to give the desired product (82 mg, 81%). LCMS calculated for $C_{12}H_{11}N_6OS_2(M+H)^+$: m/z = 319.0; Found: 319.0.

Step 2. 7-(1-aminoethyl)-3-methyl-6-(1,3-thiazol-4-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



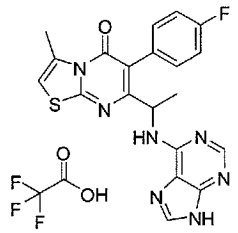
To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-(1,3-thiazol-4-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.030 g, 0.094 mmol) in tetrahydrofuran (0.3 mL) and water (0.068 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.113 mL, 0.113 mmol) at room temperature and the mixture was stirred at room temperature for 1 hour. To the mixture was added ethyl acetate and the mixture was extracted with 1 N HCl two times. The combined extracts were neutralized with solid sodium bicarbonate, and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step. LCMS calculated for $C_{12}H_{13}N_4OS_2(M+H)^+$: m/z = 293.1; Found: 293.0.

Step 3. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-(1,3-thiazol-4-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

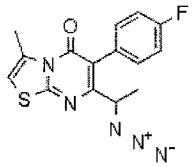


A mixture of 6-bromo-9H-purine (0.038 g, 0.19 mmol), 7-(1-aminoethyl)-3-methyl-6-(1,3-thiazol-4-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.028 g, 0.096 mmol), and *N,N*-diisopropylethylamine (0.033 mL, 0.19 mmol) in ethanol (0.3 mL) was heated at reflux under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the product as a TFA salt. LCMS calculated for $C_{17}H_{15}N_8OS_2(M+H)^+$: m/z = 411.1; Found: 411.0.

Example 22. 6-(4-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



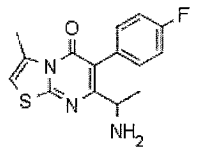
Step 1. 7-(1-azidoethyl)-6-(4-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.32 mmol) and 4-fluorophenylboronic acid (53 mg, 0.38 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate in water (0.38 mL, 0.38 mmol) and

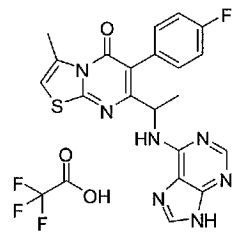
tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.016 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, and concentrated. The crude mixture was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to give the desired product (69 mg, 66%). LCMS calculated for $C_{15}H_{13}FN_5OS(M+H)^+$: m/z = 330.1; Found: 330.0.

Step 2. 7-(1-aminoethyl)-6-(4-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a stirred solution of 7-(1-azidoethyl)-6-(4-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.062 g, 0.19 mmol) in tetrahydrofuran (0.6 mL) and water (0.14 mL,) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.226 mL, 0.226 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. To the mixture was added ethyl acetate, and then the mixture was extracted with 1 N HCl two times. The combined extracts were neutralized with solid sodium bicarbonate and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step. LCMS calculated for $C_{15}H_{15}FN_3OS(M+H)^+$: m/z = 304.1; Found: 304.1.

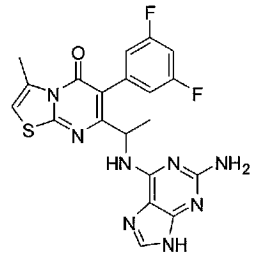
Step 3. 6-(4-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



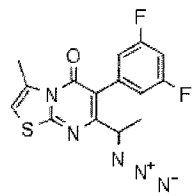
A mixture of 6-bromo-9H-purine (0.076 g, 0.38 mmol), 7-(1-aminoethyl)-6-(4-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.058 g, 0.19 mmol), and *N,N*-

diisopropylethylamine (0.066 mL, 0.38 mmol) in ethanol (0.6 mL) was heated at reflux under nitrogen overnight. The mixture was evaporated, and the resultant residue was purified on RP-HPLC (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the product as a TFA salt. LCMS calculated for $C_{20}H_{17}FN_7OS(M+H)^+$: m/z = 422.1; Found: 422.1.

Example 23. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



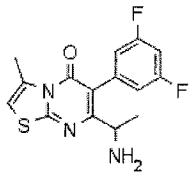
Step 1. 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (1.24 g, 3.95 mmol) and (3,5-difluorophenyl)boronic acid (0.748 g, 4.74 mmol) in 1,4-dioxane (25 mL) was added a 1 N solution of sodium carbonate in water (5.92 mL, 5.92 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.27 g, 0.24 mmol). The mixture was heated at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel (0-40% EtOAc/Hex) to give the desired product (0.42 g, 31%). LCMS calculated for $C_{15}H_{12}F_2N_5OS(M+H)^+$: m/z = 348.1; Found: 348.0. The product was subjected to chiral HPLC

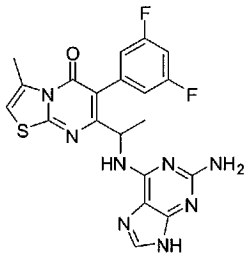
separation (ChiralPak IA Column: 20 x 250 mm, 5 μm; Mobile Phase: 5% Ethanol – 95% Hexanes; Flow Rate: 15 mL/min) to give two enantiomers. On analytic HPLC (ChiralPak IA Column: 4.6 x 250 mm, 5 μm; Mobile Phase: 5% Ethanol-95% Hexanes; Flow Rate: 1 mL/min), the first enantiomer has retention time of 7.78 min and the second peak has retention time of 8.61 minutes.

Step 2. 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



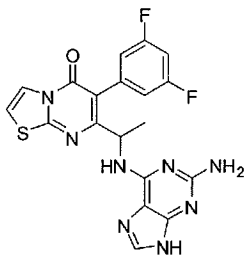
To a stirred solutions of 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.15 g, 0.43 mmol) (1 st peak from chiral separation) in tetrahydrofuran (2 mL) and water (0.5 mL) were added 1.00 M of trimethylphosphine in tetrahydrofuran (0.52 mL, 0.52 mmol) at room temperature and the mixtures were stirred at room temperature for 1 hour. To the mixture was added EtOAc and the mixture was extracted with aqueous 1 N HCl solution (three times). The combined extracts were neutralized with solid Na_2CO_3 and extracted with dichloromethane (two times). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the desired product (134 mg, 96.6%). LCMS calculated for $C_{15}H_{14}F_2N_3OS(M+H)^+$: m/z = 322.1; Found: 322.0.

Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

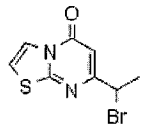


A mixture of optical pure 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.13 g, 0.40 mmol) made from above, 2-amino-6-bromopurine (0.10 g, 0.47 mmol), and *N,N*-diisopropylethylamine (0.085 mL, 0.49 mmol) in ethanol (1 mL) was heated at 110 °C overnight. LCMS showed incomplete conversion. An additional 0.5 equivalent of 2-amino-6-bromopurine and 1.0 equivalent of *N,N*-diisopropylethylamine was added, and the mixture was stirred at 110 °C for another day. The solid was shown to be 2-amino-6-bromopurine by LCMS. The mixture was filtered, and the filtrates were purified on preparative-LCMS ((XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product (0.095 g, 52%). LCMS calculated for $C_{20}H_{17}F_2N_8OS(M+H)^+$: m/z = 455.1; Found: 455.1 ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67 (1H, s), 7.27 (1H, m), 7.17 (3H, m), 7.07 (1H, s), 6.89 (1H, br s), 5.45 (2H, br s), 5.03 (1H, m), 2.63 (3H, s), 1.30 (3H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -111 ppm.

Example 24. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

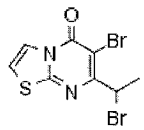


Step 1. 7-(1-bromoethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



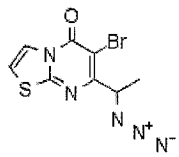
A mixture of polyphosphoric acid (73.8 g, 677 mmol), 1,3-thiazol-2-amine (12.3 g, 123 mmol), and methyl 4-bromo-3-oxopentanoate (34.8 g, 166 mmol) was stirred at 110 °C overnight. After cooling, an ice-cold 10% aq. NaOH solution was slowly added to adjust the pH to 7. The mixture was filtered, and the collected precipitate was air-dried to give crude product which was directly used in next step. LCMS calculated for $C_8H_8BrN_2OS(M+H)^+$: m/z = 259.0; Found: 259.0.

Step 2. 6-bromo-7-(1-bromoethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 7-(1-bromoethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (17.5 g, 67.5 mmol) and *N*-bromosuccinimide (14.2 g, 79.8 mmol) in acetonitrile (400 mL) was stirred at 80 °C under N_2 overnight. After removal of the solvent under reduced pressure, the resulting solid was dissolved in dichloromethane, washed sequentially with water, saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ solution and brine, dried over Na_2SO_4, and then concentrated to give crude product (3.7 g), which was used in the next step without further purification. LCMS calculated for $C_8H_7Br_2N_2OS(M+H)^+$: m/z = 336.9; Found: 336.9.

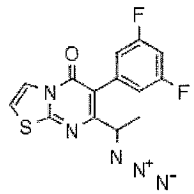
Step 3. 7-(1-azidoethyl)-6-bromo-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 6-bromo-7-(1-bromoethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (3.7 g,

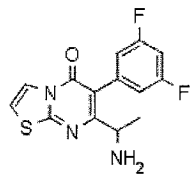
11 mmol) and sodium azide (1.4 g, 22 mmol) in *N,N*-dimethylformamide (30 mL) was stirred at room temperature for 1.5 hour. After diluted with ethyl acetate, the mixture was washed with water, dried over Na_2SO_4, concentrated and purified on silica gel (0-60% ethyl acetate/hexanes) to give the desired product (2.16 g). LCMS calculated for $C_8H_7BrN_5OS(M+H)^+$: m/z = 300.0; Found: 300.0.

Step 4. 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.50 g, 1.7 mmol) and (3,5-difluorophenyl)boronic acid (0.31 g, 2.0 mmol) in 1,4-dioxane (10 mL) was added a 1 N solution of sodium carbonate in water (2.2 mL, 2.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.096 g, 0.083 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, concentrated, and purified on silica gel (0-45% ethyl acetate/hexanes) to give the desired product (0.30 g, 53%). LCMS calculated for $C_{14}H_{10}F_2N_5OS(M+H)^+$: m/z = 334.1; Found: 334.0.

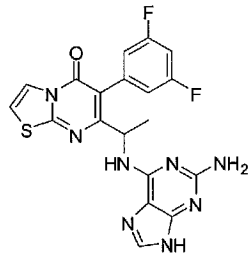
Step 5. 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a stirred solution of 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.295 g, 0.885 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (1.06 mL, 1.06 mmol) at room temperature and

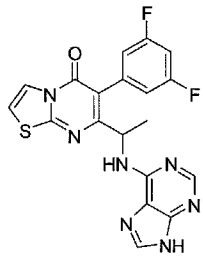
the mixture was stirred at room temperature for 1 hour. To the mixture was added ethyl acetate, and the mixture was extracted with aqueous 1 N HCl solution (three times). The combined extract was neutralized with solid $NaHCO_3$ and extracted with dichloromethane (two times). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the desired compound (0.241 g, 88.6%), which was used directly in next step. LCMS calculated for $C_{14}H_{12}F_2N_3OS(M+H)^+$: m/z = 308.1; Found: 308.0.

Step 6. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



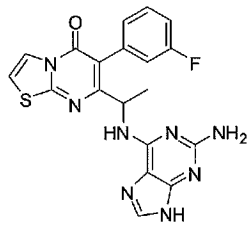
A mixture of 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.040 g, 0.13 mmol), 2-amino-6-bromopurine (0.056 g, 0.26 mmol), and *N,N*-diisopropylethylamine (0.045 mL, 0.26 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH), to give the desired product. LCMS calculated for $C_{19}H_{15}F_2N_8OS(M+H)^+$: m/z = 441.1; Found: 441.1.

Example 25. 6-(3,5-difluorophenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

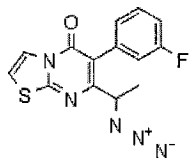


A mixture of 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.037 g, 0.12 mmol), 6-bromo-9H-purine (0.048 g, 0.24 mmol), and *N,N*-diisopropylethylamine (0.042 mL, 0.24 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{19}H_{14}F_2N_7OS(M+H)^+$: m/z = 426.1; Found: 426.0. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.99 (1H, d, J = 4.8 Hz), 7.63 (1H, s), 7.53 (1H, d, J = 4.8 Hz), 7.24 (1H, m), 7.16 (2H, m), 6.88 (1H, br s), 5.41 (2H, br s), 5.05 (1H, m), 1.27 (3H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -111 ppm.

Example 26. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



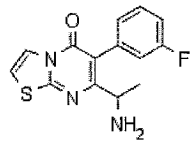
Step 1. 7-(1-azidoethyl)-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.48 g, 1.6 mmol) and (3-fluorophenyl)boronic acid (0.27 g, 2.0 mmol) in 1,4-dioxane (10 mL) was added a 1 N solution of sodium carbonate in water (2.1 mL, 2.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.092 g, 0.080 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, concentrated, and purified on silica gel (0-50% ethyl acetate/hexanes) to give the desired compound (0.32 g, 63%). LCMS calculated for $C_{14}H_{11}FN_5OS(M+H)^+$: m/z =

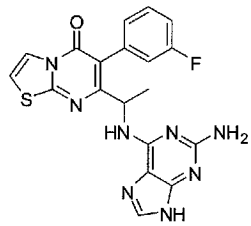
316.1; Found: 316.0.

Step 2. 7-(1-aminoethyl)-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a stirred solution of 7-(1-azidoethyl)-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.32 g, 1.0 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (1.22 mL, 1.22 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. To the mixture was added ethyl acetate, and the mixture was extracted with aqueous 1 N HCl solution (three times). The combined extract was neutralized with solid $NaHCO_3$ and extracted with dichloromethane (two times). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the desired product (0.17 g, 58%). LCMS calculated for $C_{14}H_{13}FN_3OS(M+H)^+$: m/z = 290.1; Found: 290.0.

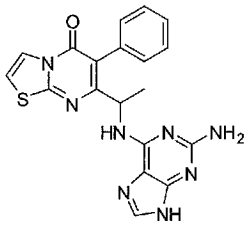
Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



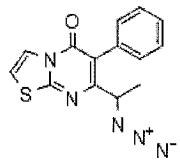
A mixture of 7-(1-aminoethyl)-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.025 g, 0.086 mmol), 2-amino-6-bromopurine (0.033 g, 0.16 mmol), and *N,N*-diisopropylethylamine (0.027 mL, 0.16 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{19}H_{16}FN_8OS(M+H)^+$: m/z = 423.1; Found: 423.0. ^1H

NMR (DMSO-d_6, 400 MHz) δ 7.98 (1H, d, J = 4.8 Hz), 7.63 (1H, s), 7.52 (1H, d, J = 4.8 Hz), 7.46 (1H, m), 7.20 (2H, m), 6.84 (1H, br s), 5.41 (1H, br s), 5.07 (1H, m), 1.26 (3H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -114 ppm.

Example 27. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

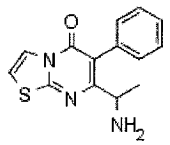


Step 1. 7-(1-azidoethyl)-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



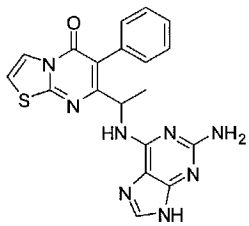
To a mixture of 7-(1-azidoethyl)-6-bromo-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.34 g, 1.1 mmol) and phenylboronic acid (0.16 g, 1.4 mmol) in 1,4-dioxane (10 mL) was added a 1 N solution of sodium carbonate in water (1.5 mL, 1.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.065 g, 0.057 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, concentrated, and purified on silica gel (0-50% ethyl acetate/hexanes) to give the desired product (0.23 g, 68%). LCMS calculated for $C_{14}H_{12}N_5OS(M+H)^+$: m/z = 298.1; Found: 298.0.

Step 2. 7-(1-aminoethyl)-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



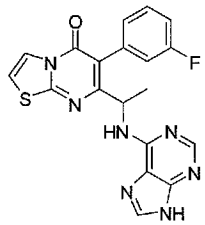
To a stirred solution of 7-(1-azidoethyl)-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.23 g, 0.77 mmol) in tetrahydrofuran (5 mL) and water (1 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.93 mL, 0.93 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. To the mixture was added ethyl acetate, and the mixture was extracted with aqueous 1 N HCl solution (three times). The combined extract was neutralized with solid $NaHCO_3$ and extracted with dicloromethane (two times). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the desired compound (0.13 g, 62%). LCMS calculated for $C_{14}H_{14}N_3OS(M+H)^+$: m/z = 272.1; Found: 272.0.

Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



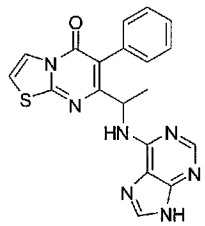
A mixture of 7-(1-aminoethyl)-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.025 g, 0.092 mmol), 2-amino-6-bromopurine (0.035 g, 0.16 mmol), and *N,N*-diisopropylethylamine (0.029 mL, 0.16 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{19}H_{17}N_8OS(M+H)^+$: m/z = 405.1; Found: 405.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 80.1 (1H, d, J = 4.8 Hz), 7.65 (1H, s), 7.55 (1H, d, J = 4.8 Hz), 7.47 (2H, m), 7.40 (3H, m), 6.79 (1H, br s), 5.48 (2H, br s), 5.13 (1H, m), 1.29 (3H, d, J = 6.8 Hz) ppm.

Example 28. 6-(3-fluorophenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



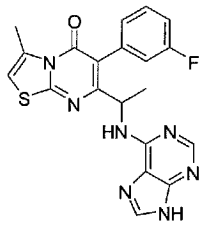
A mixture of 7-(1-aminoethyl)-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.025 g, 0.086 mmol), 6-bromo-9H-purine (0.031 g, 0.16 mmol), and *N,N*-diisopropylethylamine (0.027 mL, 0.16 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{19}H_{15}FN_7OS(M+H)^+$: m/z = 408.1; Found: 408.0.

Example 29. 6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

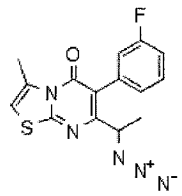


A mixture of 7-(1-aminoethyl)-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.025 g, 0.092 mmol), 6-bromo-9H-purine (0.033 g, 0.16 mmol), and *N,N*-diisopropylethylamine (0.029 mL, 0.16 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product. LCMS calculated for $C_{19}H_{16}N_7OS(M+H)^+$: m/z = 390.1; Found: 390.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.08 (1H, s), 8.06 (1H, s), 7.97 (1H, d, *J* = 4.8 Hz), 7.51 (1H, d, *J* = 4.8 Hz), 7.44~7.33 (6H, m), 5.15 (1H, m), 1.29 (3H, d, *J* = 7.2 Hz) ppm.

Example 30. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

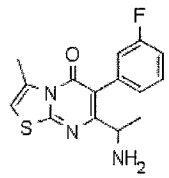


Step 1. 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



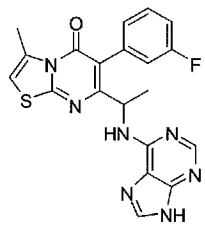
To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.50 g, 1.6 mmol) and (3-fluorophenyl)boronic acid (0.27 g, 1.9 mmol) in 1,4-dioxane (10 mL) was added 1 N solution of sodium carbonate in water (2.1 mL, 2.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.092 g, 0.080 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated and purified on silica gel (0-40% ethyl acetate/hexanes) to give the desired product (0.32 g, 61%). LCMS calculated for $C_{15}H_{13}FN_5OS(M+H)^+$: m/z = 330.1; Found: 330.0. The product was subjected to chiral HPLC separation (ChiralPak IA Column: 20 x 250 mm, 5 μm; Mobile Phase: 10% Ethanol – 90% Hexanes; Flow Rate: 18 mL/min) to give two enantiomers. On analytic HPLC (ChiralPak IA Column: 4.6 x 250 mm, 5 μm; Mobile Phase: 10% Ethanol-90% Hexanex; Flow Rate: 1 mL/min), the first enantiomer has retention time of 6.38 minutes and the second peak has retention time of 6.99 minutes.

Step 2. 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a stirred solution of 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.14 g, 0.42 mmol) (1st peak from chiral separation) in tetrahydrofuran (3 mL) and water (0.5 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.52 mL, 0.52 mmol), and the mixture was stirred at room temperature for 1 hour. To the mixtures were added ethyl acetate and the mixtures were extracted with aqueous 1 N HCl solution (three times). The combined extracts were neutralized with solid $NaHCO_3$, and extracted with dichloromethane (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the crude product (0.125 g) used directly in next step. LCMS calculated for $C_{15}H_{15}FN_3OS(M+H)^+$: m/z = 304.1; Found: 304.0.

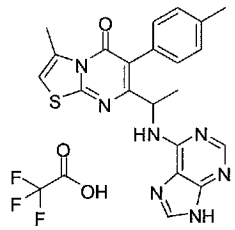
Step 3. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



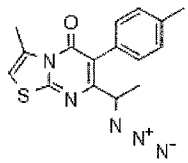
A mixture of single enantiomer 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.125 g, 0.412 mmol) made from above, 6-bromo-9H-purine (0.148 g, 0.742 mmol), and *N,N*-diisopropylethylamine (0.144 mL, 0.824 mmol) in ethanol (1.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product (0.076 g, 44%). LCMS calculated for $C_{20}H_{17}FN_7OS(M+H)^+$: m/z = 422.1; Found: 422.0. ^1H NMR (DMSO-d_6, 500 MHz) δ 8.05 (2H, s), 7.43 (1H, m), 7.24~7.14 (5H, m), 6.99 (1H, s), 5.08 (1H, m), 2.59 (3H, s),

1.29 (3H, d, J = 6.5 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -114 ppm.

Example 31. 3-methyl-6-(4-methylphenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

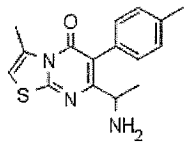


Step 1. 7-(1-azidoethyl)-3-methyl-6-(4-methylphenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.080 g, 0.25 mmol) and (4-methylphenyl)boronic acid (0.042 g, 0.31 mmol) in 1,4-dioxane (2 mL) was added 1 N solution of sodium carbonate in water (0.38 mL, 0.38 mmol) and dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium (0.011 g, 0.015 mmol). The mixture was heated at 100 °C overnight. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, concentrated and then purified on silica gel (0-25% ethyl acetate/hexane) to give the desired product (50 mg). LCMS calculated for $C_{16}H_{16}N_5OS(M+H)^+$: m/z = 326.1; Found: 326.0.

Step 2. 7-(1-aminoethyl)-3-methyl-6-(4-methylphenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a solution of 7-(1-azidoethyl)-3-methyl-6-(4-methylphenyl)-5H-[1,3]thiazolo[3,2-

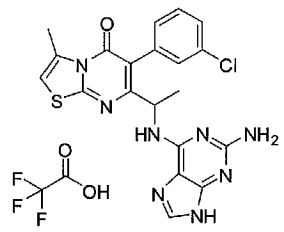
a]pyrimidin-5-one (0.050 g, 0.15 mmol) in tetrahydrofuran (2 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.23 mL, 0.23 mmol) and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give the crude product (40 mg), which was used directly in next step. LCMS calculated for $C_{16}H_{18}N_3OS(M+H)^+$: m/z = 300.1; Found: 300.1.

Step 3. 3-methyl-6-(4-methylphenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

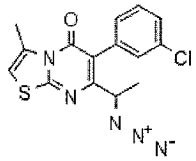


A mixture of 7-(1-aminoethyl)-3-methyl-6-(4-methylphenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.040 g, 0.13 mmol), 6-bromo-9H-purine (0.040 g, 0.20 mmol), and *N,N*-diisopropylethylamine (0.046 mL, 0.27 mmol) in ethanol (0.3 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA), to give the desired product as a TFA salt. LCMS calculated for $C_{21}H_{20}N_7OS(M+H)^+$: m/z = 418.1; Found: 418.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.57 (1H, br s), 8.39 (1H, s), 8.38 (1H, s), 7.19 (4H, s), 7.02 (1H, d, J = 1.2 Hz), 5.17 (1H, m), 2.59 (3H, s), 2.30 (3H, s), 1.32 (3H, d, J = 6.8 Hz) ppm.

Example 32. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

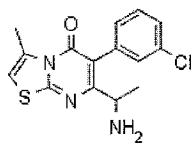


Step 1. 7-(1-azidoethyl)-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



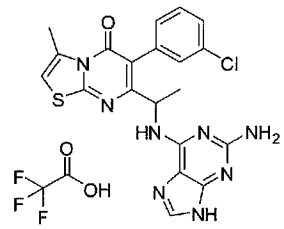
To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.12 g, 0.38 mmol) and (3-chlorophenyl)boronic acid (0.072 g, 0.46 mmol) in 1,4-dioxane (3 mL) was added a 1 N solution of sodium carbonate in water (0.5 mL, 0.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.022 g, 0.019 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated, and purified on silica gel (0-30% ethyl acetate/hexanes) to give the desired product. LCMS calculated for $C_{15}H_{13}ClN_5OS(M+H)^+$: m/z = 346.1; Found: 346.0.

Step 2. 7-(1-aminoethyl)-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



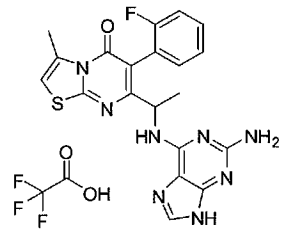
To a stirred solution of 7-(1-azidoethyl)-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.29 mmol) in tetrahydrofuran (3 mL, 40 mmol) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.35 mL, 0.35 mmol), and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give the crude product (0.090 g), which was used directly in next step. LCMS calculated for $C_{15}H_{15}ClN_3OS(M+H)^+$: m/z = 320.1; Found: 320.0.

Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

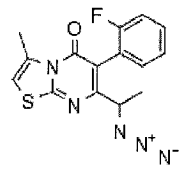


A mixture of 7-(1-aminoethyl)-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.045 g, 0.14 mmol), 2-amino-6-bromopurine (0.060 g, 0.28 mmol), and *N,N*-diisopropylethylamine (0.049 mL, 0.28 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the desired product as a TFA salt. LCMS calculated for $C_{20}H_{18}ClN_8OS(M+H)^+$: m/z = 453.1; Found: 453.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.13 (1H, s), 7.48~7.12 (8H, s), 6.55 (1H, br s), 5.14 (1H, m), 1.33 (3H, d, J = 6.8 Hz) ppm.

Example 33. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



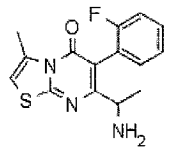
Step 1. 7-(1-azidoethyl)-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.12 g, 0.38 mmol) and (2-fluorophenyl)boronic acid (0.064 g, 0.46 mmol) in 1,4-dioxane

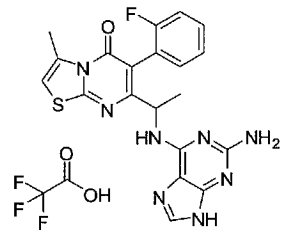
(4 mL) was added a 1 N solution of sodium carbonate in water (0.8 mL, 0.8 mmol) and dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium (0.014 g, 0.019 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated, and purified on silica gel (0-35% ethyl acetate/hexane) to give the desired product (87 mg). LCMS calculated for $C_{15}H_{13}FN_5OS(M+H)^+$: m/z = 330.1; Found: 330.0.

Step 2. 7-(1-aminoethyl)-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a stirred solution of 7-(1-azidoethyl)-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.087 g, 0.26 mmol) in tetrahydrofuran (3 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.32 mL, 0.32 mmol), and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give the crude product (0.080 g), which was used directly in next step. LCMS calculated for $C_{15}H_{15}FN_3OS(M+H)^+$: m/z = 304.1; Found: 304.0.

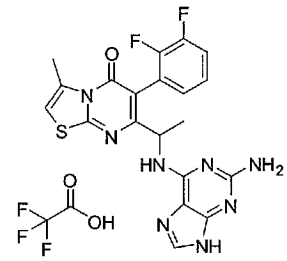
Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



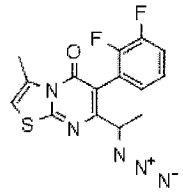
A mixture of 7-(1-aminoethyl)-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.040 g, 0.13 mmol), 2-amino-6-bromopurine (0.056 g, 0.26 mmol), and *N,N*-diisopropylethylamine (0.046 mL, 0.26 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS

(XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the desired product as a diastereoisomeric mixture (TFA salts). LCMS calculated for $C_{20}H_{18}FN_8OS(M+H)^+$: m/z = 437.1; Found: 437.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.77 (1H, br s), 8.14 (1H, m), 7.45 (2H, m), 7.28 (4H, m), 7.14 (1H, m), 5.13 (1H, m), 2.65 (3H, s), 1.42 (1.5H, d, J = 6.8 Hz), 1.28 (1.5H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -113.8, -114 ppm.

Example 34. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



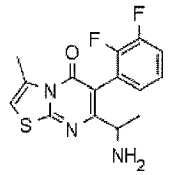
Step 1. 7-(1-azidoethyl)-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.12 g, 0.38 mmol) and (2,3-difluorophenyl)boronic acid (0.072 g, 0.46 mmol) in 1,4-dioxane (3 mL) was added a 1 N solution of sodium carbonate in water (0.57 mL, 0.57 mmol) and dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium (0.014 g, 0.019 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated, and purified on silica gel (0-30% ethyl acetate/hexane) to give the desired product (83 mg). LCMS calculated

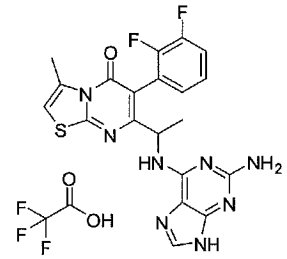
for $C_{15}H_{12}F_2N_5OS(M+H)^+$: m/z = 348.1; Found: 348.0.

Step 2. 7-(1-aminoethyl)-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a solution of 7-(1-azidoethyl)-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.083 g, 0.24 mmol) in tetrahydrofuran (3 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.29 mL, 0.29 mmol), and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give the crude product (0.076 g), which was used directly in next step. LCMS calculated for $C_{15}H_{14}F_2N_3OS(M+H)^+$: m/z = 322.1; Found: 322.0.

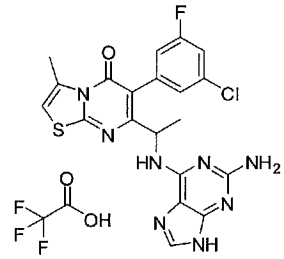
Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



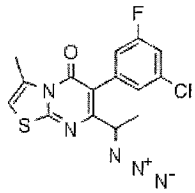
A mixture of 7-(1-aminoethyl)-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.038 g, 0.12 mmol), 2-amino-6-bromopurine (0.051 g, 0.24 mmol), and *N,N*-diisopropylethylamine (0.041 mL, 0.24 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the desired product as a mixture of two diastereomers (TFA salt). LCMS calculated for

$C_{20}H_{17}F_2N_8OS(M+H)^+$: m/z = 455.1; Found: 455.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.12 (1H, d, J = 9.6 Hz), 7.45 (1H, m), 7.30~7.23 (3H, m), 7.18~7.11 (3H, m), 6.56 (1H, s), 5.16 (1H, m), 2.66 (3H, s), 1.44 (1.5H, d, J = 6.8 Hz), 1.30 (1.5H, d, J = 6.8 Hz) ppm.

Example 35. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

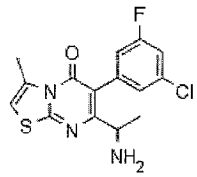


Step 1. 7-(1-azidoethyl)-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



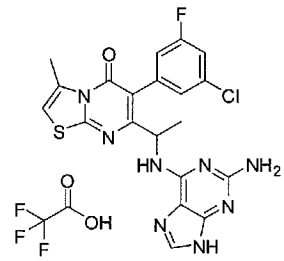
To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.12 g, 0.38 mmol) and (3-chloro-5-fluorophenyl)boronic acid (0.080 g, 0.46 mmol) in 1,4-dioxane (3 mL) was added a 1 N solution of sodium carbonate in water (0.5 mL, 0.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.022 g, 0.019 mmol). The mixture was heated at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated and purified on silica gel (0-25% ethyl acetate/hexanes) to give the desired product (0.077 g, 55%). LCMS calculated for $C_{15}H_{12}ClFN_5OS(M+H)^+$: m/z = 364.0; Found: 364.0.

Step 2. 7-(1-aminoethyl)-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



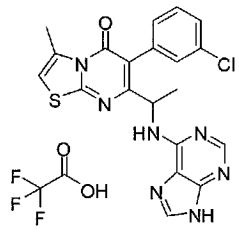
To a stirred solution of 7-(1-azidoethyl)-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.077 g, 0.21 mmol) in tetrahydrofuran (3 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.25 mL, 0.25 mmol) and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give crude product (0.070 g), which was used directly in the next step. LCMS calculated for $C_{15}H_{14}ClFN_3OS(M+H)^+$: m/z = 338.1; Found: 338.0.

Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



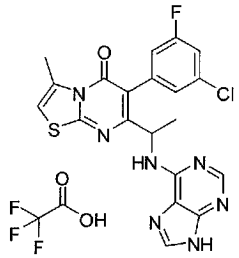
A mixture of 7-(1-aminoethyl)-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.035 g, 0.10 mmol), 2-amino-6-bromopurine (0.058 g, 0.27 mmol), and *N,N*-diisopropylethylamine (0.047 mL, 0.27 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the desired product as a TFA salt. LCMS calculated for $C_{20}H_{17}ClFN_8OS(M+H)^+$: m/z = 471.1; Found: 471.0. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.79 (1H, d, J = 7.2 Hz), 8.16 (1H, s), 7.39 (3H, m), 7.21 (2H, s), 7.18 (1H, m), 7.14 (1H, d, J = 1.2 Hz), 5.13 (1H, m), 2.65 (3H, s), 1.37 (3H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -112 ppm.

Example 36. 6-(3-chlorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



A mixture of 7-(1-aminoethyl)-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.045 g, 0.14 mmol), 6-bromo-9H-purine (0.056 g, 0.28 mmol), and *N,N*-diisopropylethylamine (0.049 mL, 0.28 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA), to give the desired product as a TFA salt. LCMS calculated for $C_{20}H_{17}ClN_7OS(M+H)^+$: m/z = 438.1; Found: 438.0. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.29 (1H, s), 7.46 (3H, m), 7.37 (1H, m), 7.08 (1H, s), 5.14 (1H, m), 2.64 (3H, s), 1.37 (3H, d, J = 6.8 Hz) ppm.

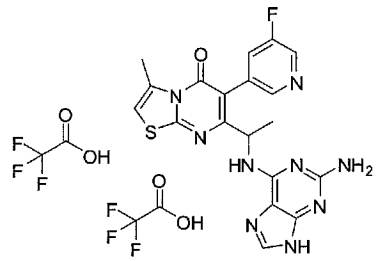
Example 37. 6-(3-chloro-5-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



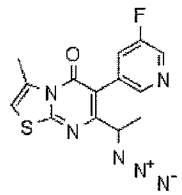
A mixture of 7-(1-aminoethyl)-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.035 g, 0.10 mmol), 6-bromo-9H-purine (0.041 g, 0.21 mmol), and *N,N*-diisopropylethylamine (0.036 mL, 0.21 mmol) in ethanol (0.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05%

TFA) to give the desired product as a TFA salt. LCMS calculated for $C_{20}H_{16}ClFN_7OS(M+H)^+$: m/z = 456.1; Found: 456.0. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.52 (1H, br s), 8.39 (1H, s), 8.36 (1H, s), 7.43 (1H, d, J = 8.0 Hz), 7.33~7.27 (3H, m), 7.10 (1H, s), 5.15 (1H, m), 2.64 (3H, s), 1.41 (3H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -112 ppm.

Example 38. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

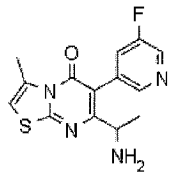


Step 1. 7-(1-azidoethyl)-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



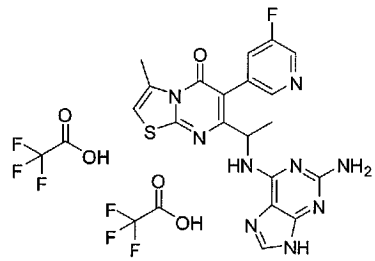
To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.12 g, 0.38 mmol) and 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.10 g, 0.46 mmol) in 1,4-dioxane (3 mL) was added a 1 N solution of sodium carbonate in water (0.57 mL, 0.57 mmol) and dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium (0.014 g, 0.020 mmol). The mixture was heated at 100 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated and purified on silica gel (0-45% ethyl acetate/hexanes) to give the desired product (0.020 g, 16%). LCMS calculated for $C_{14}H_{12}FN_6OS(M+H)^+$: m/z = 331.1; Found: 331.0.

Step 2. 7-(1-aminoethyl)-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a solution of 7-(1-azidoethyl)-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.020 g, 0.060 mmol) in tetrahydrofuran (3 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.079 mL, 0.079 mmol), and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give the crude product (0.018 g), which was used directly in next step. LCMS calculated for $C_{14}H_{14}FN_4OS(M+H)^+$: m/z = 305.1; Found: 305.0.

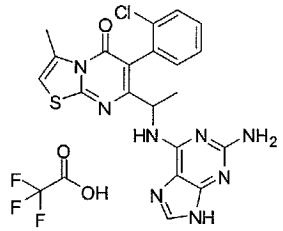
Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



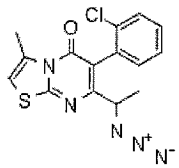
A mixture of 7-(1-aminoethyl)-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (9 mg, 0.03 mmol), 2-amino-6-bromopurine (9.5 mg, 0.044 mmol) and *N,N*-diisopropylethylamine (0.010 mL, 0.059 mmol) in ethanol (0.3 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on prep-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the desired product as a TFA salt. LCMS calculated for $C_{19}H_{17}FN_9OS(M+H)^+$: m/z = 438.1; Found: 438.0. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.82 (1H, br s), 8.59 (1H, d, J = 2.8 Hz), 8.42 (1H, s), 8.16

(1H, s), 7.77 (1H, dt, J = 9.6 and 2.4 Hz), 7.22~7.16 (4H, m), 5.08 (1H, m), 2.66 (3H, s), 1.37 (3H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -128 ppm.

Example 39. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt

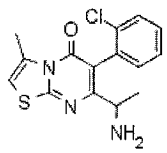


Step 1. 7-(1-azidoethyl)-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



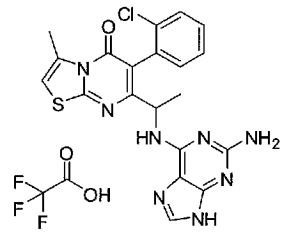
To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.12 g, 0.38 mmol) and (2-chlorophenyl)boronic acid (0.072 g, 0.46 mmol) in 1,4-dioxane (3 mL) was added a 1 N solution of sodium carbonate in water (0.57 mL, 0.57 mmol) and dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium (0.014 g, 0.019 mmol). The mixture was stirred at 105 °C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated, and purified on silica gel (0-30% ethyl acetate/hexanes) to give the desired product (0.062 g). LCMS calculated for $C_{15}H_{13}ClN_5OS(M+H)^+$: m/z = 346.1; Found: 346.0.

Step 2. 7-(1-aminoethyl)-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



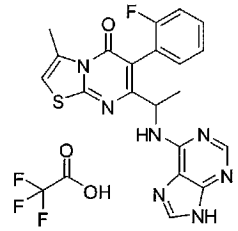
To a stirred solution of 7-(1-azidoethyl)-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.062 g, 0.18 mmol) in tetrahydrofuran (3 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.22 mL, 0.22 mmol), and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give the crude product (0.056 g), which was used directly in next step. $C_{15}H_{15}ClN_3OS(M+H)^+$: m/z = 320.1; Found: 320.0.

Step 3. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



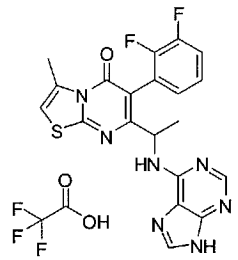
A mixture of 7-(1-aminoethyl)-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.028 g, 0.088 mmol), 2-amino-6-bromopurine (0.037 g, 0.18 mmol), and *N,N*-diisopropylethylamine (0.030 mL, 0.18 mmol) in ethanol (0.4 mL) was heated at 110 °C overnight. The mixture was filtered and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give two diastereomers as a TFA salts. On analytic HPLC (Waters SunFire C18, 2.1x50 mm, 5 μM; injection volume 2μL; flow rate 3 mL/ min; at gradient from 2% to 80% acetonitile in water conataining 0.15% NH_4OH in 3 min): First peak has retention time 1.296 min; LCMS calculated for $C_{20}H_{18}ClN_8OS(M+H)^+$: m/z = 453.1; Found: 453.0. Second peak has retention time 1.431 min; LCMS calculated for $C_{20}H_{18}ClN_8OS(M+H)^+$: m/z = 453.1; Found: 453.0.

Example 40. 6-(2-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



A mixture of 7-(1-aminoethyl)-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.040 g, 0.13 mmol), 6-bromo-9H-purine (0.052 g, 0.26 mmol), and *N,N*-diisopropylethylamine (0.046 mL, 0.26 mmol) in ethanol (0.5 mL, 8 mmol) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to give the desired product as a diasteroisomeric mixture (TFA salt). LCMS calculated for $C_{20}H_{17}FN_7OS(M+H)^+$: m/z = 422.1; Found: 422.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.50 (1H, br s), 8.40 (1H, s), 8.38 (1H, s), 7.50 (1H, m), 7.36~7.25 (3H, m), 7.10 (1H, s), 5.14 (1H, m), 2.64 (3H, s), 1.48 (1.5H, d, *J* = 6.8 Hz), 1.34 (1.5H, d, *J* = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -112, -114 ppm.

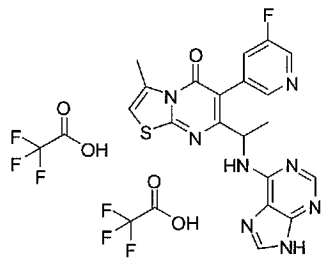
Example 41. 6-(2,3-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



A mixture of 7-(1-aminoethyl)-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.038 g, 0.12 mmol), 6-bromo-9H-purine (0.047 g, 0.24 mmol), and *N,N*-diisopropylethylamine (0.041 mL, 0.24 mmol) in ethanol (0.5 mL) was heated at 110 °C

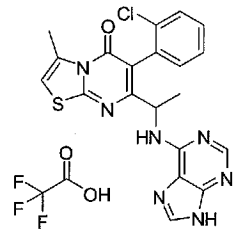
overnight. The mixture was filtered, and the filtrate was purified on prep-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA), to give the desired product as a mixture of two diastereomers (TFA salt). LCMS calculated for $C_{20}H_{16}F_2N_7OS(M+H)^+$: m/z = 440.1; Found: 440.0. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.38~8.34 (3H, m), 7.49~7.10 (4H, m), 5.12 (1H, m), 2.64 (3H, s), 1.50 (1.5H, d, J = 6.8 Hz), 1.36 (1.5H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -137.8, -139.8, -140.0 ppm.

Example 42. 6-(5-fluoropyridin-3-yl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



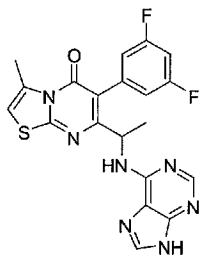
A mixture of 7-(1-aminoethyl)-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (9 mg, 0.03 mmol), 6-bromo-9H-purine (8.8 mg, 0.044 mmol), and *N,N*-diisopropylethylamine (0.010 mL, 0.059 mmol) in ethanol (0.3 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA), to give the desired product as a TFA salt. LCMS calculated for $C_{19}H_{16}FN_8OS(M+H)^+$: m/z = 423.1; Found: 423.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.60 (1H, d, J = 2.8 Hz), 8.47 (1H, s), 8.35 (1H, s), 8.33 (1H, s), 7.82 (1H, d, J = 9.6 Hz), 7.12 (1H, s), 5.09 (1H, m), 2.64 (3H, s), 1.43 (3H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -128 ppm.

Example 43. 6-(2-chlorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



A mixture of 7-(1-aminoethyl)-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.028 g, 0.088 mmol), 6-bromo-9H-purine (0.035 g, 0.18 mmol), and *N,N*-diisopropylethylamine (0.030 mL, 0.18 mmol) in ethanol (0.4 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA), to give two diastereomers as a TFA salts. On an analytic HPLC (Waters SunFire C18, 2.1x50 mm, 5 μM; injection volume 2μL; flow rate 3 mL/ min; at gradient from 2% to 80% acetonitile in water conataining 0.15% NH_4OH in 3 min): First peak has retention time 1.421 min; LCMS calculated for $C_{20}H_{17}ClN_7OS(M+H)^+$: m/z = 438.1; Found: 438.0. Second peak has retention time 1.516 min; LCMS calculated for $C_{20}H_{17}ClN_7OS(M+H)^+$: m/z = 438.1; Found: 438.0. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.36 (1H, s), 8.32 (1H, s), 7.57 (2H, m), 7.44 (2H, m), 7.11 (1H, s), 5.04 (1H, m), 2.64 (1H, s), 1.34 (3H, d, J = 6.8 Hz) ppm.

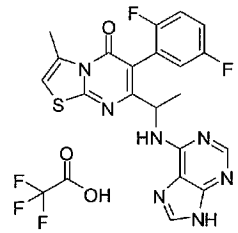
Example 44. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



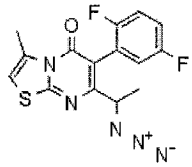
A mixture of 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.105 g, 0.327 mmol) (1st peak from Example 23, step 1 chiral separation), 6-bromo-9H-purine (0.117 g, 0.588 mmol), and *N,N*-diisopropylethylamine (0.114 mL, 0.654

mmol) in ethanol (1.5 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to give the desired product (0.073 g, 51%). LCMS calculated for $C_{20}H_{16}F_2N_7OS(M+H)^+$: m/z = 440.1; Found: 440.0. ^1H NMR (DMSO-d_6, 500 MHz) δ 8.05 (2H, s), 7.34 (1H, br s), 7.18 (1H, m), 7.12 (2H, m), 6.84 (1H, s), 7.01 (1H, s), 5.07 (1H, m), 2.43 (3H, s), 1.31 (3H, d, J = 7.0 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -111 ppm.

Example 45. 6-(2,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



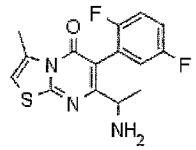
Step 1. 7-(1-azidoethyl)-6-(2,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.080 g, 0.25 mmol) and (2,5-difluorophenyl)boronic acid (0.048 g, 0.30 mmol) in 1,4-dioxane (2 mL) was added a 1 N solution of sodium carbonate in water (0.38 mL, 0.38 mmol) and dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium (0.011 g, 0.015 mmol). The mixture was stirred at 100 °C overnight. After cooled to room temperature, the mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, then concentrated and purified on silica gel (0-25% ethyl acetate/hexane) to give the desired product as a diastereoisomer mixture (54 mg). LCMS calculated for $C_{15}H_{12}F_2N_5OS(M+H)^+$: m/z = 348.1;

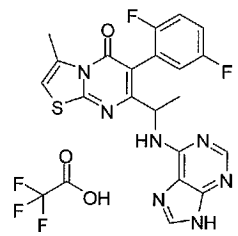
Found: 348.0.

Step 2. 7-(1-aminoethyl)-6-(2,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



To a solution of 7-(1-azidoethyl)-6-(2,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.054 g, 0.16 mmol) in tetrahydrofuran (2 mL) was added 1.00 M of trimethylphosphine in tetrahydrofuran (0.23 mL, 0.23 mmol), and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated to give the crude product (45 mg), which was used directly in the next step. LCMS calculated for $C_{15}H_{14}F_2N_3OS(M+H)^+$: m/z = 322.1; Found: 322.0.

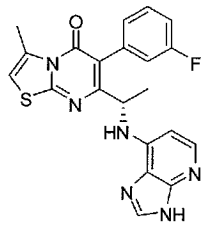
Step 3. 6-(2,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 7-(1-aminoethyl)-6-(2,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.045 g, 0.14 mmol), 6-bromo-9H-purine (0.042 g, 0.21 mmol), and *N,N*-diisopropylethylamine (0.049 mL, 0.28 mmol) in ethanol (0.3 mL) was heated at 110 °C overnight. The mixture was filtered, and the filtrate was purified on preparative-LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.05% TFA), to give the desired product as a mixture of two diastereomers (TFA salts). LCMS calculated for $C_{20}H_{16}F_2N_7OS(M+H)^+$: m/z = 440.1; Found: 440.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.64 (1H, br s), 8.38 (1H, s), 8.36 (1H, s), 7.34~7.19 (3H, m), 7.08 (1H, m), 5.06 (1H, m), 2.60 (3H, s),

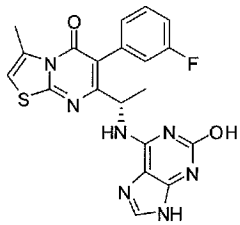
1.46 (1.5H, d, J = 6.8 Hz), 1.33 (1.5H, d, J = 6.8 Hz) ppm. ^{19}F NMR (DMSO-d_6, 376.3 MHz) δ -117.8, -119.4, -119.8, -119.9 ppm.

Example 46. 6-(3-Fluorophenyl)-7-[(1*S*)-1-(3*H*-imidazo[4,5-*b*]pyridin-7-ylamino)ethyl]-3-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one



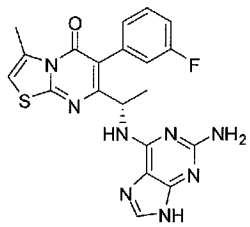
A solution of 7-[(1*S*)-1-aminoethyl]-6-(3-fluorophenyl)-3-methyl-5*H*-[1,3]thiazolo[3,2-a]pyrimidin-5-one (50 mg, 0.16 mmol), 7-chloro-3*H*-imidazo[4,5-b]pyridine (51 mg, 0.33 mmol), and *N*,*N*-diisopropylethylamine (57 μL, 0.33 mmol) in 1-butanol (0.5 mL) in a sealable vial was degassed with nitrogen, sealed, and heated at 140 °C for 48 hours. The reaction mixture was diluted with methanol and purified by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give the desired product (7 mg, 10%) as a white solid. LCMS for $C_{21}H_{18}FN_6OS$ $(M+H)^+$: m/z = 420.8. ^{1}H NMR (400 MHz, CD_3OD): δ 8.04 (s, 1 H), 7.83 (d, J = 5.9 Hz, 1 H), 7.55 - 7.49 (m, 1 H), 7.23 - 7.12 (m, 3 H), 6.86 (d, J = 1.2 Hz, 1 H), 5.96 (d, J = 5.9 Hz, 1 H), 4.69 - 4.67 (m, 1 H), 2.75 (s, 3 H), 1.57 (d, J = 6.4 Hz, 3 H).

Example 47. 6-(3-Fluorophenyl)-7-{(1*S*)-1-[(2-hydroxy-9*H*-purin-6-yl)amino]ethyl}-3-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one



Step 1. 7-{(1S)-1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5H-

[1,3]thiazolo[3,2-a]pyrimidin-5-one

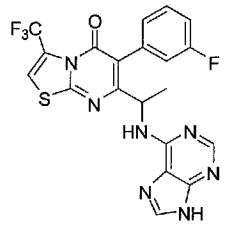


A solution of 7-[(1*S*)-1-aminoethyl]-6-(3-fluorophenyl)-3-methyl-5*H*-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.33 mmol) and 2-amino-6-bromopurine (0.11 g, 0.49 mmol) in 1-butanol (0.66 mL) was treated with *N,N*-diisopropylethylamine (86 μL, 0.49 mmol), degassed with nitrogen for 5 min and heated at 100 °C for 18 hours. The reaction was not complete and was, therefore, heated at 115 °C for an additional 5 hours. The reaction mixture was diluted with methanol (10 mL), stirred, and filtered. The filtrate was purified by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give the desired product (27 mg, 19%) as a white solid. LCMS for $C_{20}H_{18}FN_8OS$ $(M+H)^+$: m/z = 437.0.

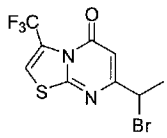
Step 2. 6-(3-Fluorophenyl)-7-{(1S)-1-[(2-hydroxy-9H-purin-6-yl)amino]ethyl}-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A solution of 7-{(1*S*)-1-[(2-amino-9*H*-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5*H*-[1,3]thiazolo[3,2-a]pyrimidin-5-one (27 mg, 62 μmol) in acetic acid (0.41 mL) and water (84 μL) at 0 °C was treated with a solution of sodium nitrite (13 mg, 0.19 mmol) in water (0.15 mL) dropwise and stirred at 0 °C for 30 minutes and at 20 °C for 16 hours. The reaction mixture was concentrated and purified by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give the desired product (7 mg, 20%) as a white solid. LCMS for $C_{20}H_{17}FN_7O_2S$ $(M+H)^+$: m/z = 437.8. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79 (br s, 1 H), 7.68-7.61 (m, 1 H), 7.50 - 7.38 (m, 3 H), 7.23 - 7.14 (m, 2 H), 7.06 (br s, 1 H), 5.02 - 4.92 (m, 1 H), 2.64 (s, 3 H), 1.26 (d, *J* = 6.7 Hz, 3 H).

Example 48. 6-(3-Fluorophenyl)-7-[1-(9*H*-purin-6-ylamino)ethyl]-3-(trifluoromethyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one

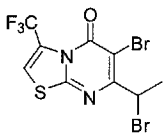


Step 1. 7-(1-Bromoethyl)-3-(trifluoromethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



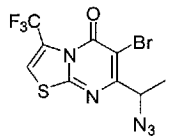
The desired compound was prepared according to the procedure of Example 8, step 2, using 4-(trifluoromethyl)-1,3-thiazol-2-amine as the starting material in 53% yield. LCMS for $C_9H_7BrF_3N_2OS$ $(M+H)^+$: m/z = 326.8, 328.8.

Step 2. 6-Bromo-7-(1-bromoethyl)-3-(trifluoromethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



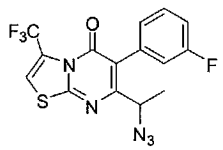
The desired compound was prepared according to the procedure of Example 8, step 3, using 7-(1-bromoethyl)-3-(trifluoromethyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one as the starting material in quantitative yield. LCMS for $C_9H_6Br_2F_3N_2OS$ $(M+H)^+$: m/z = 404.8, 406.7, 408.7.

Step 3. 7-(1-Azidoethyl)-6-bromo-3-(trifluoromethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



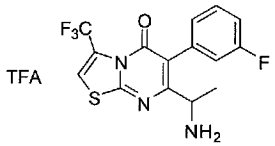
The desired compound was prepared according to the procedure of Example 8, step 4, using 6-bromo-7-(1-bromoethyl)-3-(trifluoromethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one as the starting material in 84% yield. LCMS for $C_9H_6BrF_3N_5OS$ $(M+H)^+$: m/z = 367.7, 369.8.

Step 4. 7-(1-Azidoethyl)-6-(3-fluorophenyl)-3-(trifluoromethyl)-5H-[1,3]thiazolo[3, 2-a]pyrimidin-5-one



The desired compound was prepared according to the procedure of Example 8, step 5, using 7-(1-azidoethyl)-6-bromo-3-(trifluoromethyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one and (3-fluorophenyl)boronic acid as the starting materials in 29% yield. LCMS for $C_{15}H_{10}F_4N_5OS$ $(M+H)^+$: m/z = 383.9.

Step 5. 7-(1-Aminoethyl)-6-(3-fluorophenyl)-3-(trifluoromethyl) -5H-[1,3]thiazolo[3, 2-a]pyrimidin-5-one trifluoroacetic acid salt

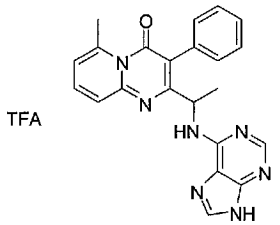


The desired compound was prepared according to the procedure of Example 8, step 6, using 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-(trifluoromethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one as the starting material in 79% yield after purification by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min). LCMS for $C_{15}H_{12}F_4N_3OS$ $(M+H)^+$: m/z = 357.9.

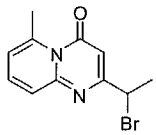
Step 6. 6-(3-Fluorophenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-3-(trifluoromethyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

The desired compound was prepared according to the procedure of Example 8, step 7, using 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-(trifluoromethyl) -5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one trifluoroacetic acid salt as the starting material in 54% yield after purification by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 30 mL/min). LCMS for $C_{20}H_{14}F_4N_7OS$ $(M+H)^+$: m/z = 475.9. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.36 (s, 1 H), 8.14 - 8.08 (m, 2 H), 7.55 - 7.46 (m, 2 H), 7.32 - 7.21 (m, 3 H), 5.19 - 5.07 (m, 1 H), 1.37 (d, *J* = 7.0 Hz, 3 H).

Example 49. 6-Methyl-3-phenyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt

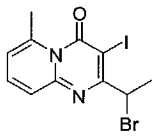


Step 1. 2-(1-Bromoethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one



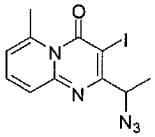
The desired compound was prepared according to the procedure of Example 8, step 2, using 6-methyl-2-pyridinamine as the starting material in 58% yield. LCMS for $C_{11}H_{12}BrN_2O$ $(M+H)^+$: m/z = 267.0, 269.0.

Step 2. 2-(1-Bromoethyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one



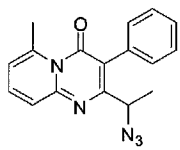
The desired compound was prepared according to the procedure of Example 8, step 3, using 2-(1-bromoethyl)-6-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one and *N*-iodosuccinimide as the starting materials in 98% yield. LCMS for $C_{11}H_{11}BrIN_2O$ $(M+H)^+$: m/z = 392.7, 394.7.

Step 3. 2-(1-Azidoethyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one



The desired compound was prepared according to the procedure of Example 8, step 4, using 2-(1-bromoethyl)-3-iodo-6-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one as the starting material in 99% yield. LCMS for $C_{11}H_{11}IN_5O$ $(M+H)^+$: m/z = 356.0.

Step 4. 2-(1-Azidoethyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

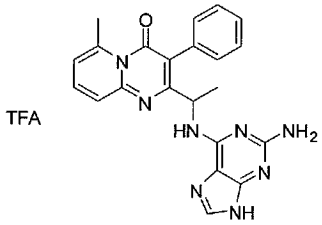


A solution of 2-(1-azidoethyl)-3-iodo-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (100 mg, 0.28 mmol) and phenylboronic acid (48 mg, 0.39 mmol) in 1,4-dioxane (2 mL) was treated with sodium carbonate (45 mg, 0.42 mmol), water (0.50 mL), and dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium (2.0 mg, 28 μmol), degassed with nitrogen for 5 minutes, and heated at 110 °C for 18 hours. The reaction mixture was purified by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min). LCMS for $C_{17}H_{16}N_5O$ $(M+H)^+$: m/z = 306.1.

Step 5. 6-Methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one trifluoroacetic acid salt

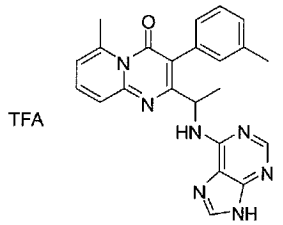
A solution of 2-(1-azidoethyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (31 mg, 0.10 mmol) in tetrahydrofuran (1 mL) and water (0.2 mL) was treated with 1 M of trimethylphosphine in tetrahydrofuran (0.20 mL, 0.20 mmol) and stirred at 20 °C for 1 hour. The reaction mixture was diluted with brine (2 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated to a crude residue. This intermediate amine was used without further purification. A solution of the amine in ethanol (1 mL) was treated with 6-bromo-9*H*-purine (31 mg, 0.16 mmol) and *N,N*-diisopropylethylamine (24 mL, 0.14 mmol) and then heated at 90 °C for 18 hours. The reaction mixture was purified by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min). LCMS for $C_{22}H_{20}N_7O$ $(M+H)^+$: m/z = 398.1.

Example 50. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-6-methyl-3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



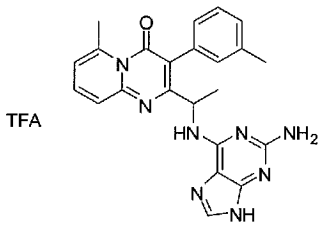
The desired compound was prepared according to the procedure of Example 49 using 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{22}H_{21}N_8O$ $(M+H)^+$: m/z = 413.0.

Example 51. 6-Methyl-3-(3-methylphenyl)-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



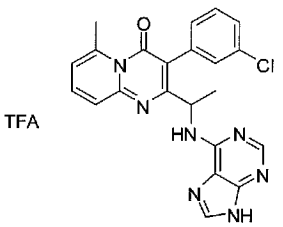
The desired compound was prepared according to the procedure of Example 49 using (3-methylphenyl)boronic acid (instead of phenylboronic acid in step 4). LCMS for $C_{23}H_{22}N_7O$ $(M+H)^+$: m/z = 411.9.

Example 52. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-6-methyl-3-(3-methylphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



The desired compound was prepared according to the procedure of Example 49 using (3-methylphenyl)boronic acid (instead of phenylboronic acid in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{23}H_{23}N_8O$ $(M+H)^+$: m/z = 427.0.

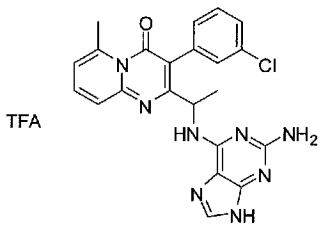
Example 53. 3-(3-Chlorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-a]pyrimidin-4-one trifluoroacetic acid salt



The desired compound was prepared according to the procedure of Example 49 using (3-

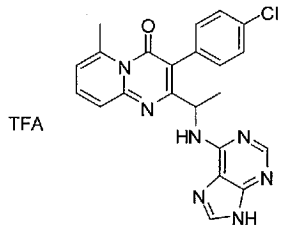
chlorophenyl)boronic acid (instead of phenylboronic acid in step 4). LCMS for $C_{22}H_{19}ClN_7O$ $(M+H)^+$: m/z = 432.1.

Example 54. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(3-chlorophenyl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



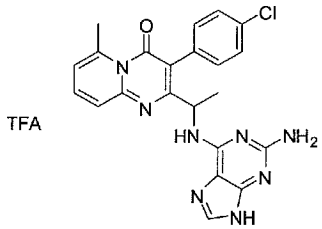
The desired compound was prepared according to the procedure of Example 49 using (3-chlorophenyl)boronic acid (instead of phenylboronic acid in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{22}H_{20}ClN_8O$ $(M+H)^+$: m/z = 447.1.

Example 55. 3-(4-Chlorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



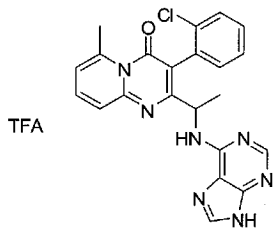
The desired compound was prepared according to the procedure of Example 49 using (4-chlorophenyl)boronic acid (instead of phenylboronic acid in step 4). LCMS for $C_{22}H_{19}ClN_7O$ $(M+H)^+$: m/z = 432.1.

Example 56. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(4-chlorophenyl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



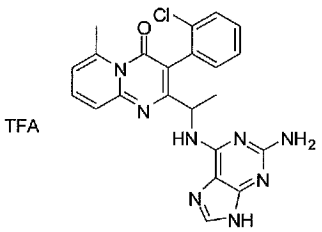
The desired compound was prepared according to the procedure of Example 49 using (4-chlorophenyl)boronic acid (instead of phenylboronic acid in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{22}H_{20}ClN_8O$ $(M+H)^+$: m/z = 447.1.

Example 57. 3-(2-Chlorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



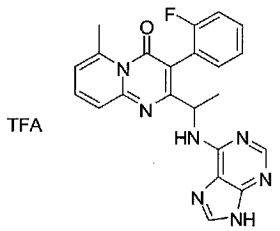
The desired compound was prepared according to the procedure of Example 49 using (2-chlorophenyl)boronic acid (instead of phenylboronic acid in step 4) as a mixture of atropisomers. LCMS for $C_{22}H_{19}ClN_7O$ $(M+H)^+$: m/z = 432.1.

Example 58. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(2-chlorophenyl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



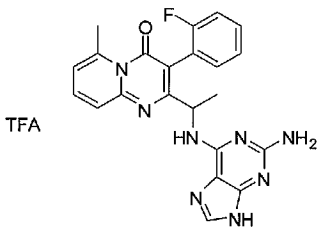
The desired compound was prepared according to the procedure of Example 49 using (2-chlorophenyl)boronic acid (instead of phenylboronic acid in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5) as a mixture of atropisomers. LCMS for $C_{22}H_{20}ClN_8O$ $(M+H)^+$: m/z = 447.1.

Example 59. 3-(2-Fluorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



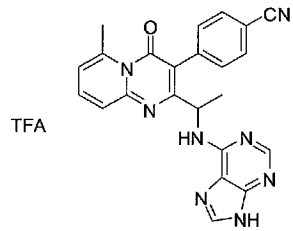
The desired compound was prepared according to the procedure of Example 49 using (2-fluorophenyl)boronic acid (instead of phenylboronic acid in step 4). LCMS for $C_{22}H_{19}FN_7O$ $(M+H)^+$: m/z = 416.1.

Example 60. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(2-fluorophenyl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



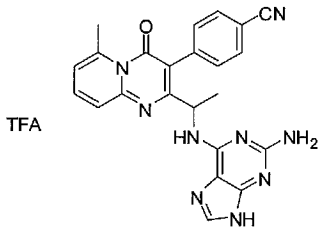
The desired compound was prepared according to the procedure of Example 49 using (2-fluorophenyl)boronic acid (instead of phenylboronic acid in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{22}H_{20}FN_8O$ $(M+H)^+$: m/z = 431.1.

Example 61. 4-{6-Methyl-4-oxo-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl}benzonitrile trifluoroacetic acid salt



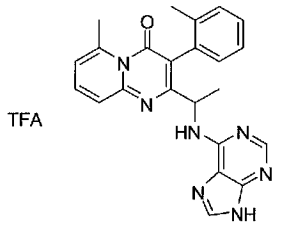
The desired compound was prepared according to the procedure of Example 49 using (4-cyanophenyl)boronic acid (instead of phenylboronic acid in step 4). LCMS for $C_{23}H_{19}N_8O$ $(M+H)^+$: m/z = 423.1.

Example 62. 4-(2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)benzonitrile trifluoroacetic acid salt



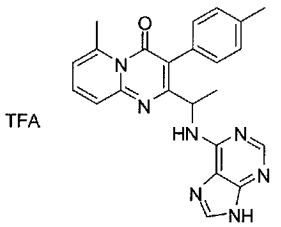
The desired compound was prepared according to the procedure of Example 49 using (4-cyanophenyl)boronic acid (instead of phenylboronic acid in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{23}H_{20}N_9O$ $(M+H)^+$: m/z = 438.2.

Example 63. 6-Methyl-3-(2-methylphenyl)-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



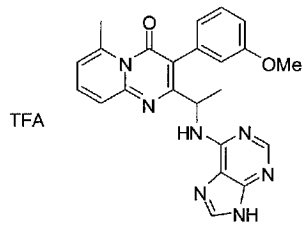
The desired compound was prepared according to the procedure of Example 49 using (2-methylphenyl)boronic acid (instead of phenylboronic acid in step 4), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and potassium carbonate (instead of sodium carbonate in step 4). LCMS for $C_{23}H_{22}N_7O$ $(M+H)^+$: m/z = 412.1.

Example 64. 6-Methyl-3-(4-methylphenyl)-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



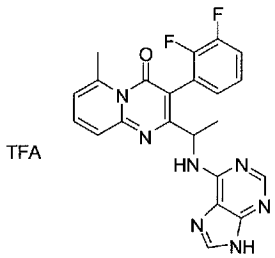
The desired compound was prepared according to the procedure of Example 49 using (4-methylphenyl)boronic acid (instead of phenylboronic acid in step 4), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and potassium carbonate (instead of sodium carbonate in step 4). LCMS for $C_{23}H_{22}N_7O$ $(M+H)^+$: m/z = 412.1.

Example 65. 3-(3-Methoxyphenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



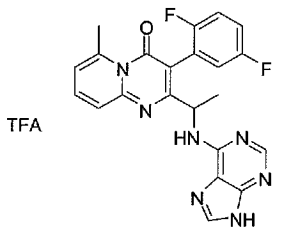
The desired compound was prepared according to the procedure of Example 49 using 3-methoxyphenylboronic acid (instead of phenylboronic acid in step 4), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and potassium carbonate (instead of sodium carbonate in step 4). LCMS for $C_{23}H_{22}N_7O_2$ $(M+H)^+$: m/z = 428.1.

Example 66. 3-(2,3-Difluorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



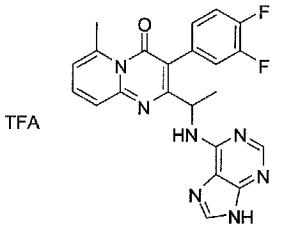
The desired compound was prepared according to the procedure of Example 49 using (2,3-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and potassium carbonate (instead of sodium carbonate in step 4). LCMS for $C_{22}H_{18}F_2N_7O$ $(M+H)^+$: m/z = 434.2.

Example 67. 3-(2,5-Difluorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



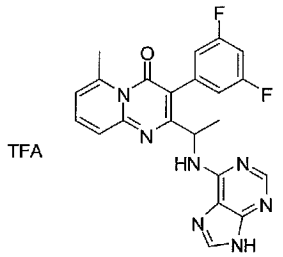
The desired compound was prepared according to the procedure of Example 49 using (2,5-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and potassium carbonate (instead of sodium carbonate in step 4). LCMS for $C_{22}H_{18}F_2N_7O$ $(M+H)^+$: m/z = 434.1.

Example 68. 3-(3,4-Difluorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



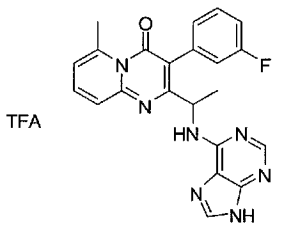
The desired compound was prepared according to the procedure of Example 49 using (3,4-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and potassium carbonate (instead of sodium carbonate in step 4). LCMS for $C_{22}H_{18}F_2N_7O$ $(M+H)^+$: m/z = 434.0.

Example 69. 3-(3,5-Difluorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



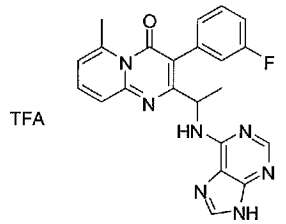
The desired compound was prepared according to the procedure of Example 49 using (3,5-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4) and tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4). LCMS for $C_{22}H_{18}F_2N_7O$ $(M+H)^+$: m/z = 434.0. ^1H NMR (300 MHz, DMSO-d_6): δ 8.80 (br s, 1 H), 8.48 (s, 2 H), 7.71 (dd, *J* = 7.9, 7.6 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 7.24 (d, *J* = 9.7, 9.1 Hz, 1 H), 7.18 - 7.11 (m, 3 H), 6.97 (d, *J* = 6.7 Hz, 1 H), 5.29 - 5.20 (m, 1 H), 2.89 (s, 3 H), 1.46 (d, *J* = 6.7 Hz, 3 H).

Example 70. 3-(3-Fluorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt

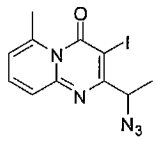


The desired compound was prepared according to the procedure of Example 49 using (3-fluorophenyl)boronic acid (instead of phenylboronic acid in step 4) and tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4). LCMS for $C_{22}H_{19}FN_7O$ $(M+H)^+$: m/z = 416.1. ^1H NMR (300 MHz, DMSO-d_6): δ 8.85 (br s, 1 H), 8.50 (s, 2 H), 7.70 (dd, *J* = 7.9, 7.6 Hz, 1 H), 7.51 - 7.40 (m, 2 H), 7.27 - 7.16 (m, 3 H), 6.96 (d, *J* = 6.7 Hz, 1 H), 5.31 - 5.20 (m, 1 H), 2.88 (s, 3 H), 1.44 (d, *J* = 6.7 Hz, 3 H).

Example 71 and Example 72. Single enantiomers of 3-(3-Fluorophenyl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt

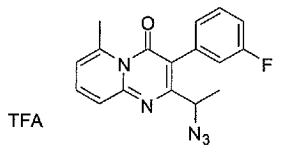


Step 1. Chiral separation of 2-(1-Azidoethyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one



The racemic mixture of 2-(1-azidoethyl)-3-iodo-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was separated by HPLC (Chiracel OJ-H, eluting with 30% ethanol/70% hexanes, at flow rate of 20 mL/min) to give the two individual enantiomers (retention times = 21.6 min, 27.2 min). Both peaks were advanced to the next step.

Step 2. Single enantiomers of 2-(1-azidoethyl)-3-(3-fluorophenyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one trifluoroacetic acid salt

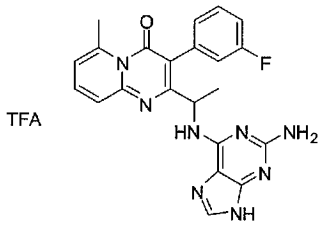


The desired compounds were prepared according to the procedure of Example 49, step 4, using peak 1 and peak 2 of 2-(1-azidoethyl)-3-iodo-6-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one and (3-fluorophenyl)boronic acid as the starting materials after purification by RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 60 mL/min). From peak 1: LCMS for $C_{17}H_{15}FN_5O$ $(M+H)^+$: m/z = 324.1. From peak 2: LCMS for $C_{17}H_{15}FN_5O$ $(M+H)^+$: m/z = 323.9.

Step 3. Single enantiomers of 3-(3-Fluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one trifluoroacetic acid salt

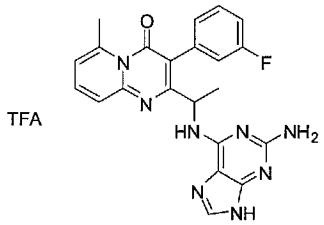
The desired compounds were prepared according to the procedure of Example 49, step 5, using the single enantiomers of 2-(1-azidoethyl)-3-(3-fluorophenyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one trifluoroacetic acid salt and (3-fluorophenyl)boronic acid as the starting materials. Example 71 (from peak 1): LCMS for $C_{22}H_{19}FN_7O$ $(M+H)^+$: m/z = 415.9.; ^1H NMR (400 MHz, DMSO-d_6): δ 8.78 (br s, 1 H), 8.48 (s, 2 H), 7.70 (dd, J = 7.8, 7.7 Hz, 1 H), 7.50 - 7.41 (m, 2 H), 7.28 - 7.17 (m, 3 H), 6.96 (d, J = 7.0 Hz, 1 H), 5.30 - 5.21 (m, 1 H), 2.88 (s, 3 H), 1.44 (d, J = 6.7 Hz, 3 H). Example 72 (from peak 2): LCMS for $C_{22}H_{19}FN_7O$ $(M+H)^+$: m/z = 416.1.; ^1H NMR (400 MHz, DMSO-d_6): δ 8.78 (br s, 1 H), 8.48 (s, 2 H), 7.70 (dd, J = 8.1, 7.5 Hz, 1 H), 7.50 - 7.42 (m, 2 H), 7.27 - 7.18 (m, 3 H), 6.96 (d, J = 6.8 Hz, 1 H), 5.30 - 5.21 (m, 1 H), 2.88 (s, 3 H), 1.44 (d, J = 6.7 Hz, 3 H).

Example 73. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(3-fluorophenyl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



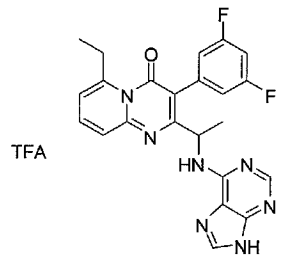
The desired compound was prepared according to the procedure of Example 49 using (3-fluorophenyl)boronic acid (instead of phenylboronic acid in step 4), tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{22}H_{20}FN_8O$ $(M+H)^+$: m/z = 431.2. ^1H NMR (300 MHz, DMSO-d_6): δ 8.72 (d, J = 7.3 Hz, 1 H), 8.17 (s, 1 H), 7.74 - 7.68 (m, 1 H), 7.50 - 7.41 (m, 2 H), 7.29 - 7.14 (m, 5 H), 6.98 (d, J = 6.4 Hz, 1 H), 5.26 - 5.17 (m, 1 H), 2.89 (s, 3 H), 1.37 (d, J = 6.7 Hz, 3 H).

Example 74 and Example 75. Single enantiomers of 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(3-fluorophenyl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



The desired compounds were prepared according to the procedure of Example 71 and 72. 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). Example 74 (from peak 1): $C_{22}H_{20}FN_8O$ $(M+H)^+$: m/z = 431.0; ^1H NMR (400 MHz, DMSO-d_6): δ 8.72 (d, *J* = 7.3 Hz, 1 H), 8.17 (s, 1 H), 7.72 (dd, *J* = 8.8, 7.1 Hz, 1 H), 7.48 - 7.40 (m, 2 H), 7.27 - 7.13 (m, 5 H), 6.98 (d, *J* = 6.8 Hz, 1 H), 5.25 - 5.18 (m, 1 H), 2.89 (s, 3 H), 1.37 (d, *J* = 6.7 Hz, 3 H). Example 75 (from peak 2): $C_{22}H_{20}FN_8O$ $(M+H)^+$: m/z = 431.1; ^1H NMR (400 MHz, DMSO-d_6): δ 8.72 (d, *J* = 7.1 Hz, 1 H), 8.17 (s, 1 H), 7.71 (dd, *J* = 8.9, 7.1 Hz, 1 H), 7.49 - 7.42 (m, 2 H), 7.28 - 7.15 (m, 5 H), 6.98 (d, *J* = 6.8 Hz, 1 H), 5.25 - 5.18 (m, 1 H), 2.89 (s, 3 H), 1.37 (d, *J* = 6.8 Hz, 3 H).

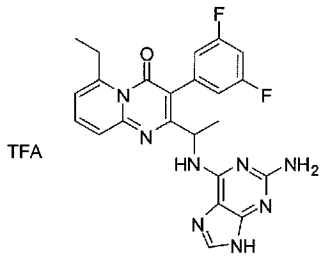
Example 76. 3-(3,5-Difluorophenyl)-6-ethyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



The desired compound was prepared according to the procedure of Example 49 using 6-ethylpyridin-2-amine (instead of 6-methyl-2-pyridinamine in step 1), *N*-bromosuccinimide

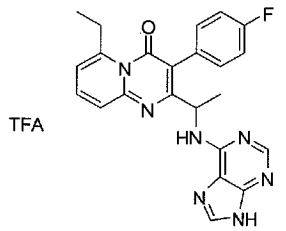
(instead of *N*-iodosuccinimide in step 2), (3,5-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4), and tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4). LCMS for $C_{23}H_{20}F_2N_7O$ $(M+H)^+$: m/z = 448.2. ^1H NMR (300 MHz, DMSO-d_6): δ 8.57 - 8.44 (m, 1 H), 8.40 (s, 2 H), 7.75 (dd, *J* = 8.2, 7.9 Hz, 1 H), 7.48 (d, *J* = 8.8 Hz, 1 H), 7.29 - 7.12 (m, 3 H), 7.04 (d, *J* = 6.7 Hz, 1 H), 5.30 - 5.17 (m, 1 H), 3.33 (q, *J* = 7.0 Hz, 2 H), 1.45 (d, *J* = 6.7 Hz, 3 H), 1.14 (t, *J* = 7.0 Hz, 3 H).

Example 77. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(3,5-difluorophenyl)-6-ethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



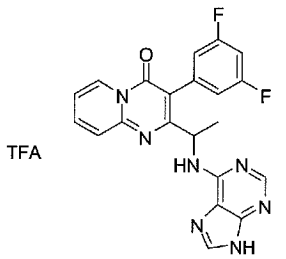
The desired compound was prepared according to the procedure of Example 49 using 6-ethylpyridin-2-amine (instead of 6-methyl-2-pyridinamine in step 1), *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (3,5-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4), tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{23}H_{21}F_2N_8O$ $(M+H)^+$: m/z = 463.2. ^1H NMR (300 MHz, DMSO-d_6): δ 8.74 - 8.69 (m, 1 H), 8.17 (s, 1 H), 7.78 (dd, *J* = 8.8, 7.0 Hz, 1 H), 7.50 (d, *J* = 8.5 Hz, 1 H), 7.32 - 7.16 (m, 3 H), 7.14 - 7.04 (m, 2 H), 5.26 - 5.16 (m, 1 H), 3.35 (q, *J* = 7.3 Hz, 2 H), 1.41 (d, *J* = 6.7 Hz, 3 H), 1.15 (t, *J* = 7.3 Hz, 3 H).

Example 78. 6-Ethyl-3-(4-fluorophenyl)-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



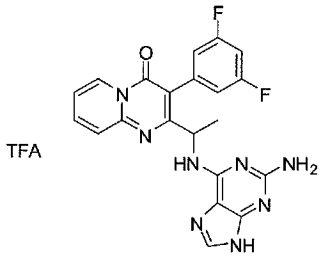
The desired compound was prepared according to the procedure of Example 49 using 6-ethylpyridin-2-amine (instead of 6-methyl-2-pyridinamine in step 1), *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (4-fluorophenyl)boronic acid (instead of phenylboronic acid in step 4), and tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4). LCMS for $C_{23}H_{21}FN_7O$ $(M+H)^+$: m/z = 430.2.

Example 79. 3-(3,5-Difluorophenyl)-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



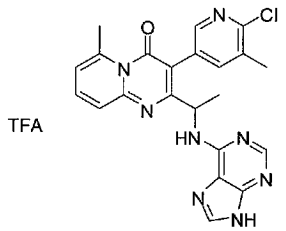
The desired compound was prepared according to the procedure of Example 49 using 2-pyridinamine (instead of 6-methyl-2-pyridinamine in step 1), *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (3,5-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4), and tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4). LCMS for $C_{21}H_{16}F_2N_7O$ $(M+H)^+$: m/z = 420.0. ^1H NMR (300 MHz, DMSO-d_6): δ 8.96 (d, *J* = 7.3 Hz, 1 H), 8.36 (s, 2 H), 8.01 (dd, *J* = 8.2, 7.3 Hz, 1 H), 7.74 (d, *J* = 8.8 Hz, 1 H), 7.40 (dd, *J* = 6.7, 6.4 Hz, 1 H), 7.32 - 7.16 (m, 3 H), 5.37 - 5.26 (m, 1 H), 1.46 (d, *J* = 6.7 Hz, 3 H).

Example 80. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(3,5-difluorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



The desired compound was prepared according to the procedure of Example 49 using 2-pyridinamine (instead of 6-methyl-2-pyridinamine in step 1), *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (3,5-difluorophenyl)boronic acid (instead of phenylboronic acid in step 4), tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4) and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{21}H_{17}F_2N_8O$ $(M+H)^+$: m/z = 435.0. ^1H NMR (300 MHz, DMSO-d_6): δ 8.98 (d, *J* = 7.0 Hz, 1 H), 8.82 - 8.72 (br s, 1 H), 8.17 (s, 1 H), 8.06 - 8.00 (m, 1 H), 7.76 (d, *J* = 9.1 Hz, 1 H), 7.43 (dd, *J* = 7.0, 5.6 Hz, 1 H), 7.30 - 7.07 (m, 5 H), 5.32 - 5.22 (m, 1 H), 1.42 (d, *J* = 6.7 Hz, 3 H).

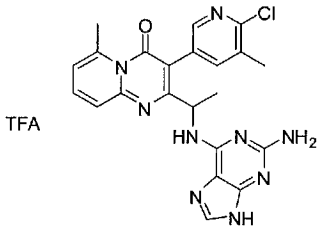
Example 81. 3-(6-Chloro-5-methylpyridin-3-yl)-6-methyl-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



The desired compound was prepared according to the procedure of Example 49 using *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (6-chloro-5-methylpyridin-3-yl)boronic acid (instead of phenylboronic acid in step 4), and tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-

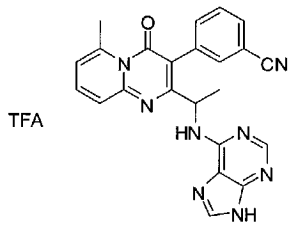
(dimethylamino)phenyl]phosphoranyl})palladium in step 4). LCMS for $C_{22}H_{20}ClN_8O$ $(M+H)^+$: m/z = 446.9. ^1H NMR (300 MHz, DMSO-d_6): δ 8.37 (br s, 2 H), 8.26 (s, 1 H), 7.82 (s, 1 H), 7.71 (dd, J = 9.1, 7.0 Hz, 1 H), 7.45 (d, J = 8.8 Hz, 1 H), 6.97 (d, J = 6.2 Hz, 1 H), 5.21 - 5.10 (m, 1 H), 2.88 (s, 3 H), 2.33 (s, 3 H), 1.45 (d, J = 6.7 Hz, 3 H).

Example 82. 2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-3-(6-chloro-5-methylpyridin-3-yl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one trifluoroacetic acid salt



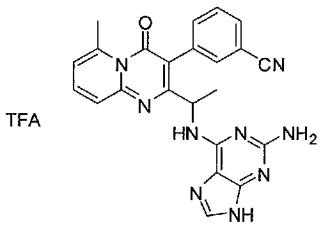
The desired compound was prepared according to the procedure of Example 49 using *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (6-chloro-5-methylpyridin-3-yl)boronic acid (instead of phenylboronic acid in step 4), tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{22}H_{21}ClN_9O$ $(M+H)^+$: m/z = 462.0. ^1H NMR (500 MHz, DMSO-d_6): δ 8.74 (br s, 1 H), 8.24 (s, 1 H), 8.18 (s, 1 H), 7.79 - 7.71 (m, 2 H), 7.50 (d, J = 8.8 Hz, 1 H), 7.29 - 7.14 (m, 2 H), 7.03 (d, J = 6.9 Hz, 1 H), 5.23 - 5.16 (m, 1 H), 2.92 (s, 3 H), 2.31 (s, 3 H), 1.43 (d, J = 6.7 Hz, 3 H).

Example 83. 3-{6-Methyl-4-oxo-2-[1-(9*H*-purin-6-ylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl}benzonitrile trifluoroacetic acid salt



The desired compound was prepared according to the procedure of Example 49 using *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (3-cyanophenyl)boronic acid (instead of phenylboronic acid in step 4), and tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4). LCMS for $C_{23}H_{19}N_8O$ $(M+H)^+$: m/z = 422.9. ^1H NMR (500 MHz, DMSO-d_6): δ 8.46 (br s, 1 H), 8.40 (s, 2 H), 7.91 - 7.83 (m, 2 H), 7.81 - 7.76 (m, 1 H), 7.75 - 7.69 (m, 1 H), 7.69 - 7.63 (m, 1 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 6.98 (d, *J* = 6.7 Hz, 1 H), 5.24 - 5.15 (br s, 1 H), 2.91 (s, 3 H), 1.46 (d, *J* = 6.6 Hz, 3 H).

Example 84. 3-(2-{1-[(2-Amino-9*H*-purin-6-yl)amino]ethyl}-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)benzonitrile trifluoroacetic acid salt



The desired compound was prepared according to the procedure of Example 49 using *N*-bromosuccinimide (instead of *N*-iodosuccinimide in step 2), (3-cyanophenyl)boronic acid (instead of phenylboronic acid in step 4), tetrakis(triphenylphosphine)palladium(0) (instead of dichloro(bis{di-*tert*-butyl[4-(dimethylamino)phenyl]phosphoranyl})palladium in step 4), and 2-amino-6-bromopurine (instead of 6-bromo-9*H*-purine in step 5). LCMS for $C_{23}H_{20}N_9O$ $(M+H)^+$: m/z = 438.0. ^1H NMR (500 MHz, DMSO-d_6): δ 8.73 (br s, 1 H), 8.18 (s, 1 H), 7.84 - 7.80 (m, 2 H), 7.78 - 7.71 (m, 2 H), 7.64 (dd, *J* = 8.2, 8.0 Hz, 1 H), 7.49 (d, *J* = 8.7 Hz, 1 H), 7.24 (br s, 2 H), 7.01 (d, *J* = 6.9 Hz, 1 H), 5.21 - 5.15 (m, 1 H), 2.92 (s, 3 H), 1.40 (d, *J* = 6.7 Hz,

3 H).

Example A1: PI3K Enzyme Assay

PI3-Kinase luminescent assay kit including lipid kinase substrate, D-myo-phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2)D (+)-sn-1,2-di-O-octanoylglyceryl, 3-O-phospho linked (PIP2), biotinylated I(1,3,4,5)P4, PI(3,4,5)P3 Detector Protein, was purchased from Echelon Biosciences (Salt Lake City, UT). AlphaScreen™ GST Detection Kit including donor and acceptor beads was purchased from PerkinElmer Life Sciences (Waltham, MA). PI3Kδ (p110δ /p85α) was purchased from Millipore (Bedford, MA). ATP, $MgCl_2$, DTT, EDTA, HEPES and CHAPS were purchased from Sigma–Aldrich (St. Louis, MO).

AlphaScreen™ Assay for PI3Kδ

The kinase reaction was conducted in 384-well REMP plate from Thermo Fisher Scientific in a final volume of 40 μL. Inhibitors were first diluted serially in DMSO and added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 2%. The PI3K assays were carried out at room temperature in 50 mM HEPES, pH 7.4, 5mM $MgCl_2$, 50 mM NaCl, 5mM DTT and CHAPS 0.04%. Reactions were initiated by the addition of ATP, the final reaction mixture consisted of 20 μM PIP2, 20 μM ATP, 1.2nM PI3Kδ were incubated for 20 min. 10 μL of reaction mixture was then transferred to 5 μL 50nM biotinylated I(1,3,4,5)P4 in quench buffer: 50 mM HEPES pH 7.4, 150 mM NaCl, 10 mM EDTA, 5 mM DTT, 0.1% Tween-20, followed with the addition of 10 μL AlphaScreen™ donor and acceptor beads suspended in quench buffer containing 25nM PI(3,4,5)P3 detector protein. The final concentration of both donor and acceptor beads is 20 mg/ml. After plate sealing, the plate was incubated in a dark location at room temperature for 2 hours. The activity of the product was determined on Fusion-alpha microplate reader (Perkin–Elmer). IC_{50} determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the GraphPad Prism 3.0 software.

Example A2: PI3K Enzyme Assay

Materials: Lipid kinase substrate, phosphoinositol-4,5-bisphosphate (PIP2), was purchased from Echelon Biosciences (Salt Lake City, UT). PI3K isoforms α, β, δ and γ were

purchased from Millipore (Bedford, MA). ATP, $MgCl_2$, DTT, EDTA, MOPS and CHAPS were purchased from Sigma–Aldrich (St. Louis, MO).

The kinase reaction was conducted in clear-bottom 96-well plate from Thermo Fisher Scientific in a final volume of 24 μL. Inhibitors were first diluted serially in DMSO and added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 0.5%. The PI3K assays were carried out at room temperature in 20 mM MOPS, pH 6.7, 10 mM $MgCl_2$, 5 mM DTT and CHAPS 0.03%. The reaction mixture was prepared containing 50 μM PIP2, kinase and varying concentration of inhibitors. Reactions were initiated by the addition of ATP containing 2.2 μCi [γ-^{33}P]ATP to a final concentration of 1000 μM. The final concentration of PI3K isoforms α, β, δ and γ in the assay were 1.3, 9.4, 2.9 and 10.8 nM respectively. Reactions were incubated for 180 min and terminated by the addition of 100 μL of 1 M potassium phosphate pH 8.0, 30 mM EDTA quench buffer. A 100 μL aliquot of the reaction solution was then transferred to 96-well Millipore MultiScreen IP 0.45 μm PVDF filter plate (The filter plate was prewetted with 200 μL 100% ethanol, distilled water, and 1 M potassium phosphate pH 8.0, respectively). The filter plate was aspirated on a Millipore Manifold under vacuum and washed with 18 × 200 μL wash buffer containing 1 M potassium phosphate pH 8.0 and 1 mM ATP. After drying by aspiration and blotting, the plate was air dried in an incubator at 37 °C overnight. Packard TopCount adapter (Millipore) was then attached to the plate followed with addition of 120 μL Microscint 20 scintillation cocktail (Perkin Elmer) in each well. After the plate sealing, the radioactivity of the product was determined by scintillation counting on Topcount (Perkin–Elmer). IC_{50} determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the GraphPad Prism 3.0 software. Compounds having and IC_{50} value of 10 μM or less are considered active. See Table 1 for data related to compounds of the invention.

Example A3: PI3Kδ scintillation proximity assay

Materials

[γ-^{33}P]ATP (10mCi/mL) was purchased from Perkin–Elmer (Waltham, MA). Lipid kinase substrate, D-myo-Phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2)D (+)-sn-1,2-di-

O-octanoylglyceryl, 3-O-phospho linked (PIP2), CAS 204858-53-7, was purchased from Echelon Biosciences (Salt Lake City, UT). PI3Kδ (p110δ /p85α) was purchased from Millipore (Bedford, MA). ATP, $MgCl_2$, DTT, EDTA, MOPS and CHAPS were purchased from Sigma–Aldrich (St. Louis, MO). Wheat Germ Agglutinin (WGA) YSi SPA Scintillation Beads was purchased from GE healthcare life sciences (Piscataway, NJ).

The kinase reaction was conducted in polystyrene 384-well matrix white plate from Thermo Fisher Scientific in a final volume of 25 μL. Inhibitors were first diluted serially in DMSO and added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 0.5%. The PI3K assays were carried out at room temperature in 20 mM MOPS, pH 6.7, 10 mM $MgCl_2$, 5 mM DTT and CHAPS 0.03%. Reactions were initiated by the addition of ATP, the final reaction mixture consisted of 20 μM PIP2, 20 μM ATP, 0.2 μCi [γ-^{33}P] ATP, 4 nM PI3Kδ. Reactions were incubated for 210 min and terminated by the addition of 40 μL SPA beads suspended in quench buffer: 150mM potassium phosphate pH 8.0, 20% glycerol. 25 mM EDTA, 400 μM ATP. The final concentration of SPA beads was 1.0mg/mL. After the plate sealing, plates were shaken overnight at room temperature and centrifuged at 1800 rpm for 10 minutes, the radioactivity of the product was determined by scintillation counting on Topcount (Perkin–Elmer). IC_{50} determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the GraphPad Prism 3.0 software.

Table 1. IC_{50} data for PI3Kδ enzyme assays A1, A2, or A3*

Example	PI3Kδ[a] IC_{50} (nM)	PI3Kδ[b] IC_{50} (nM)	PI3Kα[c] IC_{50} (nM)	PI3Kβ[c] IC_{50} (nM)	PI3Kγ[c] IC_{50} (nM)
1	+++	+++			
2	++	+			
3	+++	+++			
4	+++	++			
5	+++	++			
6	+++	+++			
7	+++	++			
8	++	+			
9	+	+	++++	++++	++
10	+	+	++++	++++	++++
11	+	+	++++	++++	+++

12	+	+			
13	+	+	++++	++++	+++
14	++	++			
15	+	+	++++	++++	++++
17		+++			
18		+++			
19		+++			
20		+			
21		+			
22		++			
23		+			++++
24		++++			
25		++++			
26		+++			
27		+++			
28		++++			
29		++++			
30	+	+	++++	++++	++++
31		+++			
32		++			
33		+			
34		+			
35		++			
36		+++			
37		+++			
38		++			
39		1st peak: +++ 2nd peak: +			
40		+			
41		++			
42		+++			
43		1st peak: +++ 2nd peak: +			
44	+	+	++++	++++	++++
45		+			
46		+			
47		+++			
48		++			
49		+			
50		+			
51		+++			
52		+			
53		+++			
54		+			
55		++++			

56		++++			
57		+			
58		+			
59		+			
60		+			
61		++++			
62		+++			
63		+++			
64		+			
65		+			
66		+			
67		+			
68		+++			
69		+++			
70		++			
71		+			++++
72		++++			
73		+			
74		+			
75		++++			
76		+++			
77		++			
78		+			
79		++++			
80		+++			
81		++++			
82		++++			
83		+++			
84		++			

* "+" = <50 nM; "++" = 50-100 nM; "+++" = 100-500 nM; "++++" = >500 nM.

a. Results in this column were obtained by Assay A1, except for Examples 15, 30 and 44 which used Assay A2.

b. Results in this column were obtained by Assay A3.

c. Results in this column were obtained by Assay A2.

Example B1: B cell proliferation assay

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

The purified B cells (2×10^5/well/200 μL) were cultured in 96-well ultra-low binding plates (Corning, Corning, NY) in RPMI1640, 10% FBS and goat F(ab')2 anti-human IgM (10 μg/ml) (Invitrogen, Carlsbad, CA), in the presence of different amount of test compounds, for three days. [^{3}H]-thymidine (1 μCi/well) (PerkinElmer, Boston, MA) in PBS was then added to the B cell cultures for an additional 12 hrs before the incorporated radioactivity was separated by filtration with water through GF/B filters (Packard Bioscience, Meriden, CT) and measured by liquid scintillation counting with a TopCount (Packard Bioscience). Compounds having and IC_{50} value of 10 μM or less are considered active. See Table 2 for data related to compounds of the invention.

Table 2. IC_{50} data for B cell proliferation assay*

Example	B cell IC_{50} (nM)
1	+
2	+++
3	+
4	+
5	+
6	++
7	++++
8	+
9	+
10	+
11	+
12	+
13	+
15	+
30	+
44	+
71	+

* "+" = <50 nM; "++" = 50-100 nM; "+++" = 100-500 nM; "++++" = >500 nM.

Example B2: Pfeiffer cell proliferation assay

Pfeiffer cell line (diffuse large B cell lymphoma) was purchased from ATCC (Manassas, VA) and maintained in the culture medium recommended (RPMI and 10% FBS). To measure the anti-proliferation activity of the PI3Kδ submittals, the Pfeiffer cells were plated with the culture medium ($2x10^3$ cells / well/ per 200 μl) into 96-well ultra-low binding plates (Corning,

Corning, NY), in the presence or absence of a concentration range of test compounds. After 3-4 days, [^{3}H]-thymidine (1 μCi/well) (PerkinElmer, Boston, MA) in PBS was then added to the cell culture for an additional 12 hrs before the incorporated radioactivity was separated by filtration with water through GF/B filters (Packard Bioscience, Meridenj, CT) and measured by liquid scintillation counting with a TopCount (Packard Bioscience). See Table 3 for data related to compounds of the invention.

Table 3. IC_{50} data for Pfeiffer cell proliferation assay*

Example	IC_{50} (nM)
1	+++
2	+
3	+++
4	+++
5	++
6	+++
7	++++
8	+
9	+
10	+
11	+
12	+++
13	+
14	+++++
15	+
17	+++
18	++
19	+++++
20	++
21	++
22	+++
23	+
24	+++
25	++++
27	+++
30	+
31	+++
32	+
33	+
34	+
35	+
36	++

Example	IC_{50} (nM)
37	++
38	++
39	First peak: +++ Second peak: +
40	++
41	++
42	+++
43	First peak: +++ Second peak: +
44	+
45	++
46	+
48	++
49	++
50	+
51	+++
52	++
53	++
54	++
57	++
58	+
59	+++
60	++
62	++++
63	+++
64	++
65	++
66	+++
67	++
68	++++
69	++
70	+
71	+
72	++++
73	+
74	+
75	++++
76	+++
77	+
78	+++
80	+++
83	+++
84	+++

* "+" = <50 nM; "++" = 50-100 nM; "+++" = 100-500 nM; "++++" = 500-1000 nM;

"+++++" = >1000 nM.

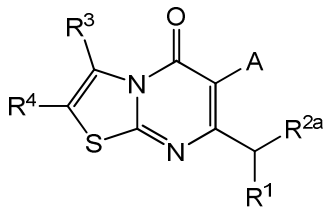
Example C: Akt phosphorylation assay

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

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

CLAIMS:

1. The compound of Formula IId:



IId

or a pharmaceutically acceptable salt thereof, wherein:

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$;

R^1 is NR^AR^B;

R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^3 and R^4 are independently selected from H, halo, CN, NO_2, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$;

R^A is bicyclic heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r\text{-}Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^B is H;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^a, R^b, R^c, and R^d are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^c and R^d together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a1}, R^{b1}, R^{c1}, and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a2}, R^{b2}, R^{c2}, and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$,

$NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a3}, R^{b3}, R^{c3}, and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{e} and R^{f} are independently selected from H, CN, NO_2, OR^{a5}, SR^{b5}, $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, and $C(O)NR^{c5}R^{d5}$;

R^{a5}, R^{b5}, R^{c5}, and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy; and

r is 0 or 1;

wherein:

heteroaryl is a monocyclic or bicyclic aromatic heterocycle having 4 to 14 ring members and 1 to 4 heteroatoms independently selected from sulfur, oxygen, and nitrogen;

bicyclic heteroaryl is a bicyclic aromatic heterocycle having 9 to 10 ring members and 1 to 4 heteroatoms independently selected from sulfur, oxygen, and nitrogen;

heterocycloalkyl is a monocyclic or bicyclic non-aromatic heterocycle having 4 to 14 ring members, wherein 1 to 4 ring members are heteroatoms independently selected from sulfur, oxygen, and nitrogen, wherein the ring-forming carbon and hateroatoms can be optionally substituted by oxo or sulfide and wherein the heterocycloalkyl group can optionally include one or more fused aromatic rings;

aryl is phenyl or naphthyl; and

cycloalkyl is a monocyclic or bicyclic non-aromatic cyclic hydrocarbon having cyclized alkyl or alkenyl groups, wherein the ring-forming atoms can be optionally substituted by oxo or sulfide and wherein the cycloalkyl group can optionally include one or more fused aromatic rings.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is phenyl.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is 6-membered heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is 5-membered heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

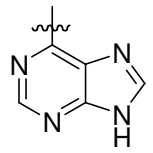
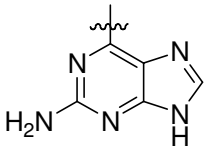
12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is pyrazolyl optionally substituted with 1 or 2 substituents independently selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from $-(C_{1-4}\text{ alkyl})_r\text{-}Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

14. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$,

$NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(=NR^{f})NR^{c5}R^{d5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

15. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^A is:

 or .

16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^{e})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e})NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

17. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^{e})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e})NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

18. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

19. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is methyl or ethyl.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is halo, CN, NO_2, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$.

21. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, halo, CN, NO_2, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, or C_{1-6} alkyl, wherein said C_{1-6} alkyl, is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a3}, SR^{a3}, $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$.

22. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is H or C_{1-6} alkyl.

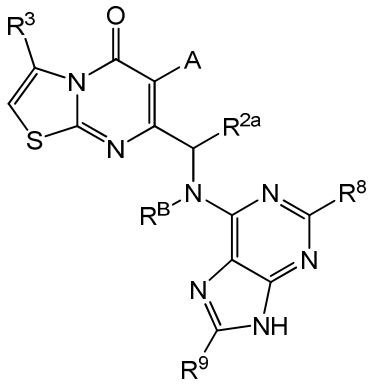
23. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} alkyl.

24. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl.

25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from H, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

26. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

27. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, having Formula IIg:



IIg

wherein R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein:

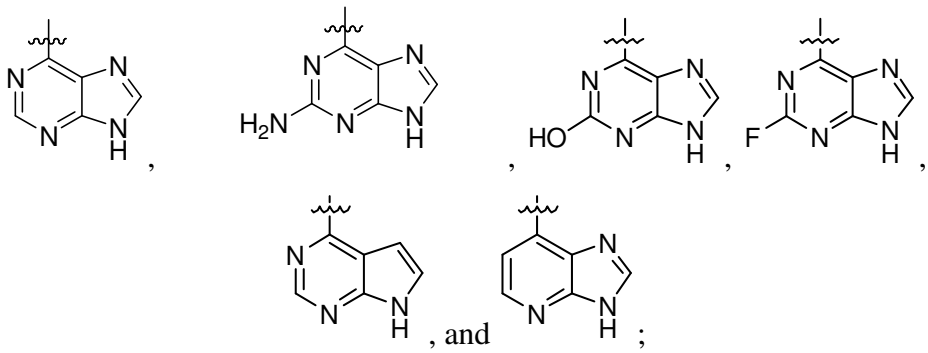
A is phenyl, 5-membered heteroaryl or 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, and OR^a;

R^1 is NR^AR^B;

R^{2a} is C_{1-6} alkyl;

$R^3$and R^4 are independently selected from H, halo, CN, NO_2, OR^{a3}, and C_{1-6} alkyl; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo;

R^A is selected from:



R^B is H;

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

each R^{a3} is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo.

29. The compound of claim 1, selected from:

3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one; and

3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one, or a pharmaceutically acceptable salt of any of the aforementioned.

30. The compound of claim 1, selected from:

6-(3,5-difluorophenyl)-3-methyl-7-[1-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3,5-difluorophenyl)-7-{1-[(2-fluoro-9H-purin-6-yl)amino]ethyl}-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-4-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-(1,3-thiazol-2-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-(1,3-thiazol-4-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(4-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3,5-difluorophenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3-fluorophenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

3-methyl-6-(4-methylphenyl)-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2,3-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-chloro-5-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3-chlorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3-chloro-5-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(5-fluoropyridin-3-yl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2-chlorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(2-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(2,3-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(5-fluoropyridin-3-yl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(2-chlorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-

a]pyrimidin-5-one;

6-(2,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3-Fluorophenyl)-7-[(1*S*)-1-(3*H*-imidazo[4,5-*b*]pyridin-7-ylamino)ethyl]-3-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one;

6-(3-Fluorophenyl)-7-{(1*S*)-1-[(2-hydroxy-9*H*-purin-6-yl)amino]ethyl}-3-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one; and

6-(3-Fluorophenyl)-7-[1-(9*H*-purin-6-ylamino)ethyl]-3-(trifluoromethyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one;

or a pharmaceutically acceptable salt of any of the aforementioned.

31. The compound of claim 1, wherein the compound is 7-(1-(9H-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one; or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1, wherein the compound is (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one; or a pharmaceutically acceptable salt thereof.

33. A composition comprising a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

34. Use of a compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for inhibiting an activity of a PI3K kinase.

35. The use of claim 34 wherein the PI3K is selected from the group consisting of PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ.

36. The use of claim 34 wherein said PI3K comprises a mutation.

37-. The use of any one of claims 34 to 36 wherein said compound is a selective inhibitor for PI3Kδ over one or more of PI3Kα, PI3Kβ, and PI3Kγ.

38. Use of a compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for treatment of a disease, wherein said disease is associated with abnormal expression or activity of a PI3K kinase.

39. The use of claim 38 wherein said disease is osteoarthritis, restenosis, atherosclerosis, bone disorders, arthritis, diabetic retinopathy, psoriasis, benign prostatic hypertrophy, inflammation, angiogenesis, pancreatitis, kidney disease, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or Sjoegren's syndrome.

40. The use of claim 38 wherein the PI3K is selected from the group consisting of PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ.

41. The use of claim 38 wherein the PI3K is PI3Kδ.

42. The use of any one of claims 38 to 41 wherein more than one of said compounds is administered.

43. The use of claim 42 wherein the compound is administered in combination with a kinase inhibitor that inhibits a kinase other than a PI3K kinase.

44. Use of a compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for treatment of an immune-based disease selected from rheumatoid arthritis, allergy, asthma, glomerulonephritis, lupus, and inflammation related to any of the aforementioned.

45. Use of a compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for treatment of a cancer selected from breast, prostate, colon, endometrial, brain, bladder, skin, uterus, ovary, lung, pancreatic, renal, gastric, and a hematological cancer.

46. The use of claim 45 wherein said hematological cancer is acute myeloblastic leukemia, chronic myeloid leukemia, or B cell lymphoma.

47. Use of a compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for treatment of a lung disease selected from acute lung injury (ALI) or adult respiratory distress syndrome (ARDS).