

METHODS OF TREATING DISEASES AND DISORDERS

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application No. 63/115,317, filed on November 18, 2020.

BACKGROUND

Interleukin-1 (IL-1) Receptor-Associated Kinase 4 (IRAK4) is a serine/threonine kinase enzyme that plays an essential role in signal transduction by Toll/IL-1 receptors (TIRs). Diverse IRAK enzymes are key components in the signal transduction pathways mediated by interleukin-1 receptor (IL-1R) and Toll-like receptors (TLRs) (Janssens, S, et al. Mol. Cell. 11, 2003, 293–302). There are four members in the mammalian IRAK family: IRAK1, IRAK2, IRAK3 and IRAK4. These proteins are characterized by a typical N-terminal death domain that mediates interaction with MyD88-family adaptor proteins and a centrally located kinase domain. The IRAK proteins, as well as MyD88, have been shown to play a role in transducing signals other than those originating from IL-1R receptors, including signals triggered by activation of IL-18 receptors (Kanakaraj, et al. J. Exp. Med. 189(7):1999, 1129-38) and LPS receptors (Yang, et al., J. Immunol. 163, 1999, 639-643). Out of four members in the mammalian IRAK family, IRAK4 is considered to be the “master IRAK”. Under overexpression conditions, all IRAKs can mediate the activation of nuclear factor- κ B (NF- κ B) and stress-induced mitogen activated protein kinase (MAPK)-signaling cascades. However, only IRAK-1 and IRAK4 have been shown to have active kinase activity. While IRAK-1 kinase activity could be dispensable for its function in IL-1-induced NF- κ B activation (Kanakaraj et al, J. Exp. Med. 187(12), 1998, 2073–2079) and (Xiaoxia Li, et al. Mol. Cell. Biol. 19(7), 1999, 4643–4652), IRAK4 requires its kinase activity for signal transduction (Li S, et al. Proc. Natl. Acad. Sci. USA 99(8), 2002, 5567–5572) and (Lye, E et al, J. Biol. Chem. 279(39); 2004, 40653-8). Given the central role of IRAK4 in Toll-like/IL-1R signalling and immunological protection, IRAK4 inhibitors have been implicated as valuable therapeutics in inflammatory diseases, sepsis and autoimmune disorders (Wietek C, et al, Mol. Interv. 2: 2002, 212–215).

Mice lacking IRAK4 are viable and show complete abrogation of inflammatory cytokine production in response to IL-1, IL-18 or LPS (Suzuki et al. Nature, 416(6882), 2002, 750-756). Similarly, human patients lacking IRAK4 are severely immune-compromised and are not responsive to these cytokines (Medvedev et al. J. Exp. Med., 198(4), 2003, 521-531

and Picard et al. *Science* 299(5615), 2003, 2076-2079). Knock-in mice containing inactive IRAK4 were completely resistant to lipopolysaccharide- and CpG-induced shock (Kim TW, et al. *J Exp Med* 204: 2007, 1025 -36) and (Kawagoe T, et al. *J Exp Med* 204(5): 2007, 1013-1024) and illustrated that IRAK4 kinase activity is essential for cytokine production, activation of MAPKs and induction of NF- κ B regulated genes in response to TLR ligands (Koziczak-Holbro M, et al. *J Biol Chem*; 282(18): 2007;13552-13560). Inactivation of IRAK4 kinase (IRAK4 KI) in mice leads to resistance to EAE due to reduction in infiltrating inflammatory cells into CNS and reduced antigen specific CD4⁺ T-cell mediated IL-17 production (Kirk A et al. *The Journal of Immunology*, 183(1), 2009, 568-577).

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in adults with approximately 78 thousand new cases and 20 thousand deaths estimated for 2020 in the United States. The molecular pathology driving NHL is varied, although a common theme is over activity of the NF- κ B signaling pathway. Specific molecular changes have been identified that drive this pathway in subsets of NHL. For example, Diffuse large B-cell lymphoma (hereafter also referred to as "DLBCL") is an aggressive lymphoma that can arise in lymph nodes or outside of the lymphatic system, in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. DLBCL is a cancer of B cells, a type of white blood cell responsible for producing antibodies. It is the most common type of non-Hodgkin's lymphoma among adults, with an annual incidence of 7–8 cases per 100,000 people per year. This cancer occurs primarily in older individuals, with a median age of diagnosis at approximately 70 years of age, though it can also occur in children and young adults in rare cases. DLBCL is an aggressive tumor and the first sign of this illness is typically the observation of a rapidly growing mass. The five-year survival rate is only 58%. DLBCL has subtypes that are named according to their cell of origin and include germinal center B-cell-like (GCB) and activated B-cell-like (ABC). They differ in having a worse prognosis and, in some cases, requiring particularized approaches to treatment.

Another example of a NHL is Waldenstrom's macroglobulinemia (WM). WM is a non-Hodgkin's lymphoma that affects two types of B cells, lymphoplasmacytoid cells and plasma cells. WM is characterized by having high levels of a circulating antibody, immunoglobulin M (IgM), which is made and secreted by the cells involved in the disease. WM is a rare disease, with only about 1,500 cases per year in the United States. There is no single accepted treatment for WM and a marked variation in clinical outcome due to gaps in knowledge of the disease's

molecular basis. Objective response rates are high (> 80%) but complete response rates are low (0–15%).

Other types of non-Hodgkin's lymphoma include mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), CNS lymphoma, and testicular lymphoma. Non-Hodgkin's lymphoma can be caused by a variety of factors such as infections agents (Epstein-Barr virus, hepatitis C virus and human T-Cell leukemia virus), radiation and chemotherapy treatments, and autoimmune diseases. As a group, non-Hodgkin's lymphoma affects 2.1% of the US population during their life. The percentage of people who survive beyond five years after diagnosis is 71%.

In view of the foregoing, there is a clear and unmet need for additional therapies for the treatment of cancers and other diseases associated with IRAK4.

SUMMARY OF THE INVENTION

In certain aspects, the present disclosure provides methods of treating a disease or disorder in a subject comprising:

obtaining a biological sample from the subject;

measuring an expression of a phosphorylated NF- κ B in the biological sample;

comparing the level of expression of the phosphorylated NF- κ B to a level of expression of phosphorylated NF- κ B in a reference; and

administering an IRAK4 modifying compound selected from an IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression of a phosphorylated NF- κ B is elevated as compared to the level of expression of phosphorylated NF- κ B in the reference.

In certain aspects, the present disclosure provides methods for detecting elevated expression of phosphorylated NF- κ B p50 (p-p50) in a biological sample comprising:

contacting the biological sample with a first antibody specific for NF- κ B p-p50, thereby

providing an antibody-NF- κ B p-p50 conjugate;

contacting the antibody-NF- κ B p-p50 conjugate with a second antibody thereby providing an antibody/antibody conjugate mixture, wherein the second antibody is specific for the first antibody and the second antibody has enzymatic activity;

treating the antibody/antibody conjugate mixture with a chromogenic substrate for the enzymatic activity, thereby providing a substrate/antibody/anti-bodyconjugate mixture; and
counterstaining the substrate/antibody/anti-bodyconjugate mixture.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a dose-dependent objective response to a human patient receiving Compound 1 at certain dosages.

FIG. 2 is a schematic of the IRAK1/4 Complex with adapter protein MYD88. After substrate binding to IL-R1 or TLR, MYD88 activation recruits IRAK4/1 complex allowing IRAK-1 phosphorylation. Phosphorylated IRAK-1 then binds to TRAF-6 activating NF- κ B signaling causing inflammation and tumor promotion. MYD88-L265P mutation leads to sustained upregulation of this pathway. Compound 1 inhibits IRAK4.

FIG. 3 shows a dose-dependent objective response to a human patient receiving Compound 1 at certain dosages.

FIG. 4 shows the response of certain human patients who received Compound 1.

FIGs. 5A-C show the efficacy of Compound 1 against certain *in vivo* models of non-Hodgkin's lymphoma. In each instance, administration of Compound 1 reduced tumor growth.

FIG. 6 shows the efficacy of Compound 1 in combination with ibrutinib. The combination of Compound 1 and ibrutinib demonstrated synergistic reduction of tumor growth as compared to either Compound 1 or ibrutinib alone.

FIG. 7 shows the oral pharmacological profile of exemplary dosages of Compound 1 in humans. After oral administration, Compound 1 is rapidly absorbed with maximum plasma concentrations observed at 0.5-8 hours post dose. Compound 1 exhibits dose-proportional increase in exposure and has a half-life of approximately 6 hours. Minimal to no accumulation is observed following multiple daily single dose administration. Moderate accumulation is observed at steady state following multiple daily twice dose administration. In summary, the oral pharmacokinetics of Compound 1 are desirable.

FIG. 8 shows the percentage reduction in tumor burden for subjects who received 300mg BID. Compound 1 has an acceptable safety and tolerability profile at RP2D, including 3 patients who have been on the study 1-2 years.

FIG. 9A shows the effects of exemplary concentrations of Compound 1 on erythroid differentiation from Primary MDS/AML Hematopoietic Stem and Progenitor Cells (HSCPs).

FIG. 9B shows the effects of exemplary concentrations of Compound 1 on neutrophilic differentiation from Primary MDS/AML Hematopoietic Stem and Progenitor Cells (HSCPs).

FIG. 10A shows the effects of Compound 1 on spleen weight in leukemic xerographs following 6 weeks of treatment at 12.5 mg/kg.

FIG. 10B shows the effects of Compound 1 on liver weight in leukemic xerographs following 6 weeks of treatment at 12.5 mg/kg.

FIG. 10C shows the effects of Compound 1 on the % of leukemic cells in the bone marrow in leukemic xerographs following 6 weeks of treatment at 12.5 mg/kg. Compound 1 decreased the disease burden in THP-1 xerographs.

FIG. 11 illustrates the design of the student described in Example 4.

FIG. 12A shows the effects of Compound 1 on NF- κ B phospho-p50 expression. NF- κ B phospho-p50 protein expression in pre-treatment biopsies correlated with Lymphoma Shrinkage or Stable Disease. SD refers to stable disease and PD refers to progressive disease.

FIG. 12B shows the effects of Compound 1 on NF- κ B phospho-p50 expression. Inhibition of NF- κ B phospho-p50 expression indicates Compound 1 is inhibiting IRAK4 and downregulating NF- κ B. During treatment with Compound 1, NF- κ B phospho-p50 expression is inhibited (positive changes to negative).

FIG. 12C shows the expression of NF- κ B phospho-p50 expression in human tonsil cells and lymphoma cells. Expression of NF- κ B phospho-p50 is increased in lymphoma cells.

FIG. 13A is a Western blot of OCL-LY10 cells treated with DMSO or Compound 1. Treatment with Compound 1 downregulated the expression of NF- κ B phospho-p50.

FIG. 13B is a Western blot of AML cells treated with DMSO or Compound 1. Treatment with Compound 1 downregulated the expression of NF- κ B phospho-p50.

FIG. 14A-B are representative pictures of FFPE BM samples obtained from AML patients showing the expression of NF- κ B p-p50 in the samples.

DETAILED DESCRIPTION OF THE INVENTION

Activation of IRAK4 leads to activation of NF- κ B signaling pathway including phosphorylation of NF- κ B p50 which is required for DNA binding and transcriptional activity of NF- κ B (Hou S et al. Phosphorylation of serine 337 of NF- κ B p50 is critical for DNA binding. *J Biol Chem*. 2003). Elevated cellular expression levels of NF- κ B p-p50 and activation of NF- κ B are indicative of expression of biologically active IRAK4 in the cell.

In one aspect, the present disclosure provides methods of treating a disease or disorder in a subject comprising:

obtaining a biological sample from the subject;
measuring an expression of a phosphorylated NF- κ B in the biological sample;
comparing the level of expression of the phosphorylated NF- κ B to a level of expression of phosphorylated NF- κ B in a reference; and
administering an IRAK4 modifying compound selected from an IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression of a phosphorylated NF- κ B is elevated as compared to the level of expression of phosphorylated NF- κ B in the reference.

In another aspect, the present disclosure provides methods of treating an IRAK4 mediated disease or disorder in a subject comprising:

obtaining a biological sample from the subject;
measuring an expression of a phosphorylated NF- κ B in the biological sample;
comparing the level of expression of the phosphorylated NF- κ B to a level of expression of phosphorylated NF- κ B in a reference; and
administering an IRAK4 modifying compound selected from an IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression of a phosphorylated NF- κ B is elevated as compared to the level of expression of phosphorylated NF- κ B in the reference.

In yet another aspect, the present disclosure provides methods of treating a disease or disorder in a subject comprising:

obtaining a biological sample from the subject;
measuring an expression of a phosphorylated NF- κ B in the biological sample;
comparing the level of expression of the phosphorylated NF- κ B to a level of expression of phosphorylated NF- κ B in a reference; and
administering a drug that is not an IRAK4 modifying compound to the subject if the expression of a phosphorylated NF- κ B is not elevated as compared to the level of expression of phosphorylated NF- κ B in the reference.

In certain embodiments, the aforementioned methods further comprise obtaining the reference. In certain embodiments, the reference is a value obtained from a subject or a plurality of subjects that does not suffer from the disease or disorder. In certain preferred embodiments,

the value is obtained from the same biological source (e.g., tissue, blood, or other bodily fluid) as the biological sample. In certain embodiments, the value is obtained from tissue or blood.

In certain preferred embodiments, the phosphorylated NF- κ B is NF- κ B p-p50. In certain preferred embodiments, the methods comprise administering the IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression of NF- κ B p-p50 is elevated. In certain embodiments, the expression of NF- κ B p-p50 is nuclear expression. In certain embodiments, the expression of NF- κ B p-p50 is cytoplasmic expression. In certain embodiments, the expression of NF- κ B p-p50 is the combination of nuclear expression and cytoplasmic expression.

In certain preferred embodiments, the phosphorylated NF- κ B is NF- κ B p-p65. In certain preferred embodiments, the methods comprise administering the IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression of NF- κ B p-p65 is elevated. In certain embodiments, the expression of NF- κ B p-p65 is nuclear expression. In certain embodiments, the expression of NF- κ B p-p65 is cytoplasmic expression. In certain embodiments, the expression of NF- κ B p-p65 is the combination of nuclear expression and cytoplasmic expression.

In another aspect, the present disclosure provides methods for detecting elevated expression of NF- κ B p-p50 in a biological sample comprising
contacting the biological sample with a first antibody specific for NF- κ B p-p50, thereby
providing an antibody-NF- κ B p-p50 conjugate;
contacting the antibody-NF- κ B p-p50 conjugate with a second antibody thereby providing an
antibody/anti-bodyconjugate mixture, wherein the second antibody is specific for the
first antibody and the second antibody has enzymatic activity;
treating the antibody/anti-bodyconjugate mixture with a chromogenic substrate for the
enzymatic activity, thereby providing a substrate/antibody/anti-bodyconjugate
mixture; and
counterstaining the substrate/antibody/anti-bodyconjugate mixture.

In certain embodiments, counterstaining the substrate/antibody/anti-bodyconjugate mixture is performed for no more than 60 seconds. In certain embodiments, counterstaining the substrate/antibody/antibodyconjugate mixture is performed for no more than 10 seconds.

In certain embodiments, the counterstain is hematoxylin.

In certain embodiments, the enzymatic activity is peroxidase activity. In certain embodiments, the chromogenic substrate is a peroxidase substrate.

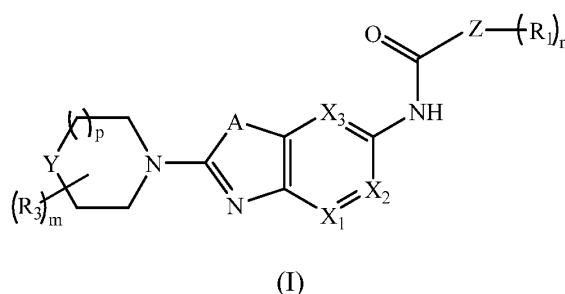
In other embodiments, the enzymatic activity is alkaline phosphatase activity. In certain embodiments, the chromogenic substrate is a phosphatase substrate.

In certain embodiments, the first antibody is a monoclonal antibody. In certain embodiments, the second antibody is a monoclonal antibody.

IRAK4 Inhibitors

Broadly speaking, the methods disclosed herein may be performed with any IRAK4 inhibitor. For example, the methods may be performed using IRAK4 inhibitors disclosed in PCT/IB2015/050119, PCT/IB2015/050217, PCT/IB2015/0054620, PCT/IB2016/054203, and/or PCT/IB2016/054229; the contents of each of the aforementioned international applications is fully incorporated by reference herein.

In certain embodiments, the IRAK4 inhibitor is represented by formula I:



or a pharmaceutically acceptable salt thereof;

wherein

X₁ and X₃ independently are CH or N; X₂ is CR₂ or N; provided one and not more than one of

X₁, X₂ or X₃ is N;

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or -NR_aR_b;

R₂ is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or -NR_aR_b; wherein the substituent is alkyl, amino, halo or hydroxyl;

R₃, at each occurrence, is alkyl or hydroxyl;

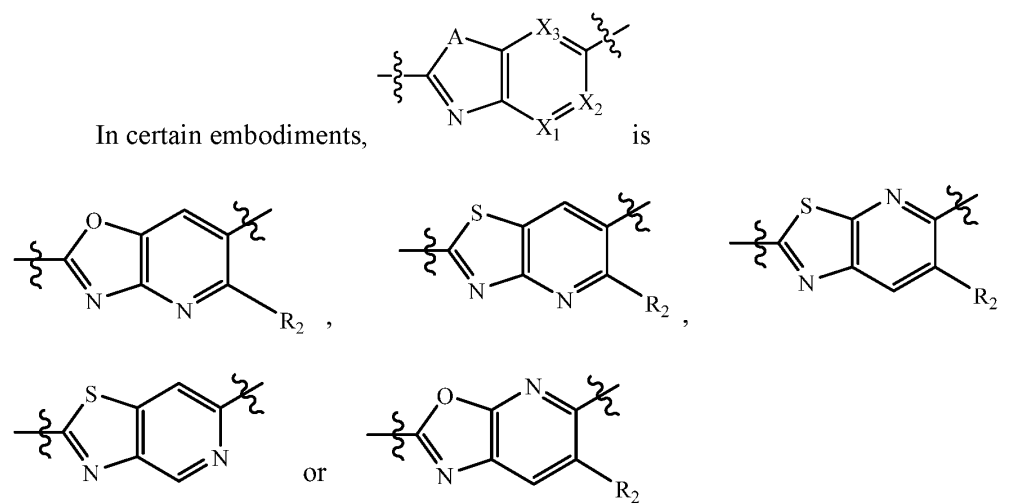
R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

'm' and 'n' are independently 0, 1 or 2;

'p' is 0 or 1.

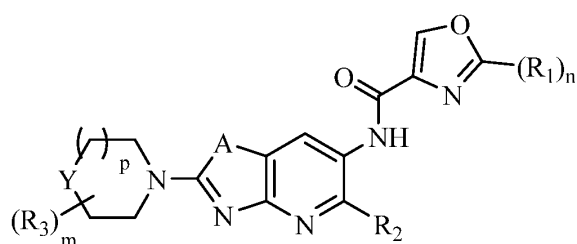
In certain embodiments, A is O or S; Y is -CH₂- or O; Z is aryl or heterocyclyl; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; 'm' is 0; and 'n' is 1.

In other embodiments, A is O or S; Y is -CH₂- or O; Z is aryl or heterocyclyl; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; 'm' and 'n' are independently 0, 1 or 2; and 'p' is 0 or 1.



In certain embodiments, Z is aryl or 5- or 6-membered heterocyclyl. In certain embodiments, Z is an optionally substituted heterocyclyl selected from phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl and azabicyclo[3.2.1]octanyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; and R_a and R_b are independently hydrogen, alkyl or acyl.

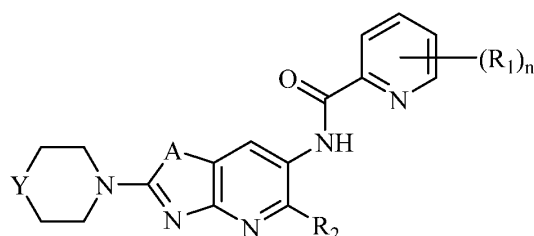
In certain embodiments, the IRAK4 inhibitor is represented by formula (IA):



(IA)

or a pharmaceutically acceptable salt thereof. In certain embodiments, A is O or S; Y is -CH₂- or O; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; 'm' is 0; and 'n' is 1. In other embodiments, A is O or S; Y is -CH₂- or O; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and 'm' and 'n' are independently 0, 1 or 2.

In certain embodiments, the IRAK4 inhibitor is represented by formula (IB):

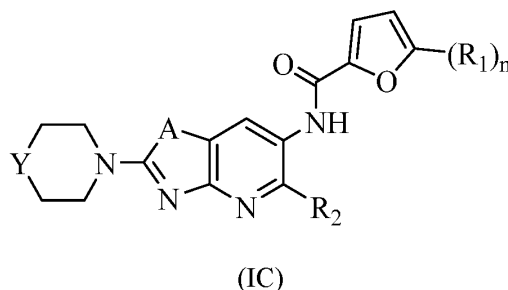


(IB)

or a pharmaceutically acceptable salt thereof. In certain embodiments, A is O or S; Y is -CH₂- or O; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; and 'n' is 1. In other embodiments, A is O or S; Y is -CH₂- or O; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -

NR_aR_b , where the substituent is selected from amino, halo or hydroxyl; and 'm' and 'n' are independently 0, 1 or 2.

In certain embodiments, the IRAK4 inhibitor is represented by formula (IC):



or a pharmaceutically acceptable salt thereof.

In certain embodiments, R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $\text{-NR}_a\text{R}_b$; and R_a and R_b are independently hydrogen or acyl. In other embodiments, R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, aminoalkyl, halo, or $\text{-NR}_a\text{R}_b$; and R_a and R_b are independently hydrogen or acyl. In yet other embodiments, R_1 is optionally substituted heterocyclyl; and the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or $\text{-NR}_a\text{R}_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl. In certain embodiments, R_1 is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl. In certain embodiments, R_1 is optionally substituted pyrazolyl, wherein the substituent is alkyl, hydroxyl or $\text{-NR}_a\text{R}_b$. In other embodiments, R_1 is halo.

In certain embodiments, R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $\text{-NR}_a\text{R}_b$, where the substituent is selected from amino, halo or hydroxyl. In certain embodiments, R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $\text{-NR}_a\text{R}_b$, where the substituent is selected from amino, halo or hydroxyl. In certain embodiments, R_2 is optionally substituted heterocyclyl selected from piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidiny, pyrazolyl, furanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is hydroxyl, halo, alkyl or amino. In certain embodiments, R_2 is piperidinyl, pyrrolidinyl, morpholinyl, or piperazinyl. In other embodiments, R_2 is hydrogen. In yet other embodiments, R_2 is cycloalkyl. In certain embodiments, R_2 is cyclopropyl.

In certain embodiments, R_3 is alkyl.

In certain embodiments, m is 0 and p is 1. In other embodiments, m is 0 or 2, and p is 0 or 1.

In certain embodiments, the IRAK4 inhibitor is selected from:

6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide hydrochloride;

N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-chloro-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide;

2-(2-chloropyridin-4-yl)-N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(2-morpholinothiazolo[4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;

2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-dimorpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(3-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methylpyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide hydrochloride;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide hydrochloride;

N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methoxypyridin-4-yl)oxazole-4-carboxamide;

2-(6-methoxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;

N-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-aminopyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;

N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-acetamidopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

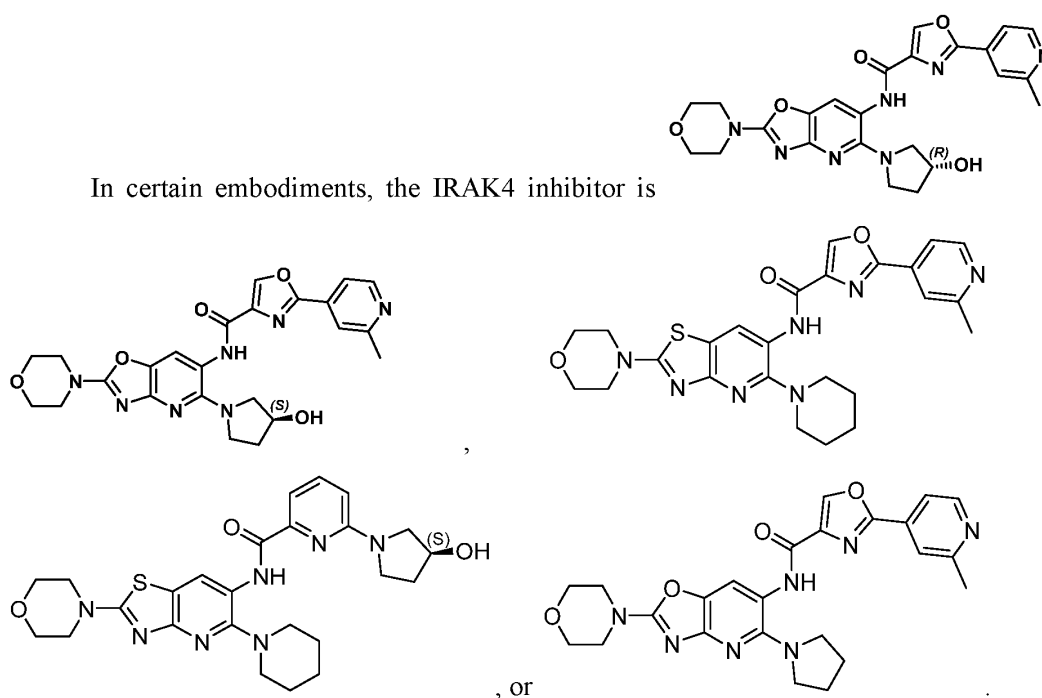
2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

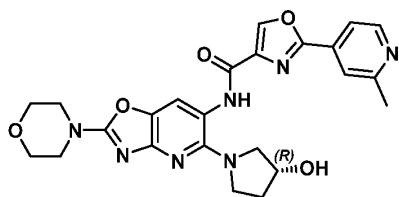
5-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)furan-3-carboxamide hydrochloride;

2-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
 2-(2-aminopyridin-4-yl)-N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
 N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
 N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
 N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride; and
 N-(5-(2-hydroxypyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
 or a pharmaceutically acceptable salt or a stereoisomer thereof.

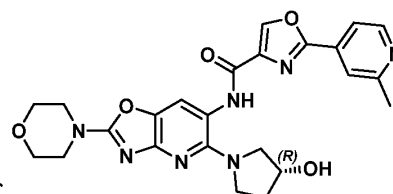
In certain embodiments, the IRAK4 inhibitor is



In certain preferred embodiments, the IRAK4 inhibitor is



(Compound 1). In other preferred embodiments, the



IRAK4 inhibitor is a pharmaceutically acceptable salt of

Compound 1 may be administered in any amount or manner that elicits the desired response in the subject. For example, 100 – 400 mg of Compound 1 can be administered to the subject twice per day or 200 – 1000 mg of Compound 1 can be administered to the subject once per day. In certain embodiments, 100 – 400 mg of Compound 1 is administered to the subject twice per day. In certain embodiments, 200 – 400 mg of Compound 1 is administered to the subject twice per day. In certain preferred embodiments, 250 – 350 mg of Compound 1 is administered to the subject twice per day. In certain embodiments, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of Compound 1 is administered to the subject twice per day. In certain embodiments, about 50 mg, about 75 mg, about 100 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, or about 400 mg of Compound 1 is administered to the subject twice per day. In certain embodiments, about 50 mg, about 100 mg, about 200 mg, or about 300 mg of Compound 1 is administered to the subject twice per day. In certain embodiments, about 50 mg of Compound 1 is administered to the subject twice per day. In other embodiments, about 200 mg of Compound 1 is administered to the subject twice per day. In other embodiments, about 225 mg of Compound 1 is administered to the subject twice per day. In other embodiments, about 250 mg of Compound 1 is administered to the subject twice per day. In other embodiments, about 275 mg of Compound 1 is administered to the subject twice per day. In particularly preferred embodiments, about 300 mg of Compound 1 is administered to the subject twice per day. In other embodiments, about 325 mg of Compound 1 is administered to the subject twice per day. In other embodiments, about 350 mg of

Compound 1 is administered to the subject twice per day. In other embodiments, about 375 mg of Compound 1 is administered to the subject twice per day. In other embodiments, about 400 mg of Compound 1 is administered to the subject twice per day.

In certain embodiments, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of Compound 1 to the subject once per day. In certain embodiments, about 50 mg of Compound 1 to the subject once per day. In certain embodiments, about 75 mg of Compound 1 to the subject once per day. In certain embodiments, about 100 mg of Compound 1 to the subject once per day. In certain embodiments, about 125 mg of Compound 1 to the subject once per day. In certain embodiments, about 150 mg of Compound 1 to the subject once per day.

In certain preferred embodiments, Compound 1 is orally administered to the subject. In certain embodiments, about 50 mg of Compound 1 is orally administered to the subject twice per day. In other embodiments, about 200 mg of Compound 1 is orally administered to the subject twice per day. In other embodiments, about 250 mg of Compound 1 is orally administered to the subject twice per day. In particularly preferred embodiments, about 300 mg of Compound 1 is orally administered to the subject twice per day. In other embodiments, about 325 mg of Compound 1 is orally administered to the subject twice per day. In other embodiments, about 350 mg of Compound 1 is orally administered to the subject twice per day. In other embodiments, about 375 mg of Compound 1 is orally administered to the subject twice per day. In other embodiments, about 400 mg of Compound 1 is orally administered to the subject twice per day. In other embodiments, about 50 mg of Compound 1 to the subject once per day. In yet other embodiments, about 75 mg of Compound 1 to the subject once per day. In yet other embodiments, about 100 mg of Compound 1 to the subject once per day. In yet other embodiments, about 125 mg of Compound 1 to the subject once per day. In yet other embodiments, about 150 mg of Compound 1 to the subject once per day.

In other embodiments, the IRAK4 inhibitor is PF-06650833 or BAY 1830839.

IRAK4 Degradors

In certain embodiments, the method comprises administering an IRAK4 degrader. In certain embodiments, the IRAK4 degrader is KT-474.

Combination Therapies

In certain embodiments of the methods disclosed herein, the method further comprises conjointly administering a BCL-2 inhibitor to the subject. In certain preferred embodiments, the BCL-2 inhibitor is venetoclax. In certain embodiments, the method further comprises administering 400 mg of venetoclax daily. In certain embodiments, the venetoclax is administered orally. In certain preferred embodiments, the method further comprises orally administering 400 mg of venetoclax daily.

In other embodiments, the method further comprises conjointly administering a BTK inhibitor to the subject. In certain embodiments, the BTK inhibitor is ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain embodiments, the BTK inhibitor is ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain embodiments, the BTK inhibitor is acalabrutinib. In certain embodiments, the method comprises administering 200 mg of acalabrutinib daily. In certain embodiments, the acalabrutinib is administered orally. In certain embodiments, the method comprises orally administering 200 mg of acalabrutinib daily. In certain preferred embodiments, the BTK inhibitor is ibrutinib. In certain embodiments, the method comprises administering 420 mg of ibrutinib daily. In other embodiments, the method comprises administering 420 mg of ibrutinib daily. In certain embodiments, the ibrutinib is administered orally. In certain preferred embodiments, orally administering 420 mg of ibrutinib daily. In other preferred embodiments, the method comprises administering 560 mg of ibrutinib daily. In certain embodiments, the BTK inhibitor is zanubrutinib. In certain embodiments, the method administering 160 mg of zanubrutinib twice daily. In other embodiments, the method comprises administering 320 mg of zanubrutinib once daily. In certain embodiments, the zanubrutinib is administered orally. In certain embodiments, the method comprises orally administering 160 mg of zanubrutinib twice daily. In other embodiments, the method comprises orally administering 320 mg of zanubrutinib once daily. In certain embodiments, the method further comprises conjointly administering one or more of ABT-737, BAY-1143572, 5-fluorouracil, abiraterone acetate, acetylcholine, ado-trastuzumab emtansine, afatinib, aldesleukin, alectinib, alemtuzumab, alitretinoin, aminolevulinic acid, anastrozole, anastrozole, aprepitant, arsenic trioxide, asparaginase erwinia chrysanthemi, atezolizumab, axitinib, azacitidine, belinostat, bendamustine, benzyl isothiocyanate, bevacizumab, bexarotene, bicalutamide, bleomycin, blinatumomab, bortezomib, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, capecitabine, carboplatin, carfilzomib, carmustine, ceritinib, cetuximab, chlorambucil, cisplatin, clofarabine,

cobimetinib, copanlisib, crizotinib, cyclophosphamide, cytarabine, dabrafenib, dacarbazine, dacarbazine, dactinomycin, daratumumab, dasatinib, daunorubicin, decitabine, defibrotide sodium, degarelix, denileukin diftitox, denosumab, dexamethasone, dexrazoxane, dihydrotestosterone (DHT), dinutuximab, docetaxel, doxorubicin, elotuzumab, eltrombopag, enzalutamide, epirubicin, eribulin mesylate, erlotinib, etoposide, everolimus, exemestane, exemestane, filgrastim, fludarabine phosphate, flutamide, fulvestrant, fulvestrant, gefitinib, gemcitabine, gemtuzumab, gemtuzumab ozogamicin, glucarpidase, goserelin acetate, hydroxyurea, ibritumomab tiuxetan, ibrutinib, idarubicin, idelalisib, ifosfamide, imatinib, imiquimod, interferon alfa-2b, ipilimumab, irinotecan, ixabepilone, ixazomib, lanreotide, lapatinib, lenalidomide, lenvatinib, letrozole, leucovorin, leuprolide, lomustine, mechlorethamine, megestrol acetate, melphalan, mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, navitoclax, necitumumab, nelarabine, netupitant, nilotinib, nilutamide, nivolumab, obinutuzumab, ofatumumab, olaparib, omacetaxine mepesuccinate, osimertinib, oxaliplatin, ozogamicin, paclitaxel, palbociclib, palifermin, pamidronate, panitumumab, panobinostat, pazopanib, pegaspargase, peginterferon alfa-2b, pembrolizumab, pemetrexed, pertuzumab, plerixafor, pomalidomide, ponatinib, pralatrexate, prednisone, procarbazine, propranolol, radium 223 dichloride, raloxifene, ramucirumab, rasburicase, regorafenib, rituximab, rolapitant, romidepsin, romiplostim, ruxolitinib, siltuximab, sipuleucel-t, sonidegib, sorafenib, sunitinib, talimogene laherparepvec, tamoxifen, temozolomide, temsirolimus, thalidomide, thioguanine, thiotepa, tipiracil, topotecan, toremifene, toremifene, tositumomab, trabectedin, trametinib, trastuzumab, tretinoin, trifluridine, uridine triacetate, vandetanib, vemurafenib, venetoclax, vinblastine, vincristine, vinorelbine, vismodegib, vorinostat, ziv-aflibercept, zoledronic acid, and pharmaceutically acceptable salts thereof. In some embodiments, the second therapeutic agent is one or more of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Diseases and Disorders

The methods disclosed herein relate to the treatment of many diseases and disorders; for example, the methods may be used to treat diseases and disorders related to IRAK4. In certain embodiments, the disease or disorder is a cancer, preferably a hematological malignancy, such as a leukemia or lymphoma, for example a non-Hodgkin's lymphoma. In certain embodiments, the hematological malignancy is myelogenous leukemia, myeloid leukemia (e.g., acute myeloid leukemia), myelodysplastic syndrome, lymphoblastic leukemia (e.g., acute lymphoblastic leukemia), chronic lymphocytic leukemia (CLL), small lymphocytic

lymphoma (SLL), high risk CLL, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) (e.g., DLBCL or ABC-DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, marginal zone lymphoma (MZL), Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, extranodal marginal zone B cell lymphoma, transformed high grade B-cell lymphoma (HGBL), lymphoplasmacytic lymphoma (LPL), central nervous system lymphoma (CNSL), or MALT lymphoma. In certain embodiments, the hematological malignancy is myelogenous leukemia. In other embodiments, the hematological malignancy is myeloid leukemia (e.g., acute myeloid leukemia). In certain embodiments, the hematological malignancy is acute myeloid leukemia (e.g., AML). In certain embodiments, the AML is primary AML. In other embodiments, the AML is secondary AML. In yet other embodiments, the hematological malignancy is myelodysplastic syndrome. In certain embodiments, the myelodysplastic syndrome is high grade. In other embodiments, the myelodysplastic syndrome is low grade. In certain embodiments, the myelodysplastic syndrome is high risk. In yet other embodiments, the hematological malignancy is lymphoblastic leukemia (e.g., acute lymphoblastic leukemia). In yet other embodiments, the hematological malignancy is chronic lymphocytic leukemia (CLL). In certain embodiments, the CLL is high risk CLL. In yet other embodiments, the hematological malignancy is small lymphocytic lymphoma (SLL). In yet other embodiments, the hematological malignancy is follicular lymphoma. In yet other embodiments, the hematological malignancy is diffuse large B-cell lymphoma (DLBCL). In yet other embodiments, the hematological malignancy is activated B cell-like (ABC) DLBCL. In yet other embodiments, the hematological malignancy is germinal center B cell-like (GCB) DLBCL. In certain embodiments, the DLBCL is extranodal. In certain embodiments, the DLBCL is extranodal leg lymphoma, extranodal testicle lymphoma, or extra nodal not otherwise specified (NOS) type lymphoma. In yet other embodiments, the hematological malignancy is mantle cell lymphoma. In further embodiments, the hematological malignancy is Waldenstrom's macroglobulinemia. In yet other embodiments, the hematological malignancy is multiple myeloma. In still other embodiments, the hematological malignancy is marginal zone lymphoma. In yet other embodiments, the hematological malignancy is Burkitt's lymphoma. In yet other embodiments, the hematological malignancy is non-Burkitt high grade B cell lymphoma. In still other embodiments, the hematological malignancy is extranodal marginal zone B cell lymphoma. In yet other embodiments, the hematological malignancy is transformed high grade B-cell lymphoma (HGBL). In yet other embodiments, the hematological malignancy is lymphoplasmacytic lymphoma (LPL). In yet other embodiments, the hematological

malignancy is CNS lymphoma. In yet other embodiments, the CNS lymphoma is primary CNS lymphoma (PCNSL). In yet other embodiments, the hematological malignancy is MALT lymphoma. In certain embodiments, the hematological malignancies described above may be relapsed or refractory. In certain embodiments, the hematological malignancies described above are resistant to treatment with a BTK inhibitor. In certain embodiments, the hematological malignancies described above are resistant to treatment with a BTK inhibitor as a monotherapy. In certain embodiments, the hematological malignancies is resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain preferred embodiments, the hematological malignancy is resistant to treatment with ibrutinib.

In certain embodiments, the cancer is selected from brain cancer, kidney cancer, liver cancer, stomach cancer, penile cancer, vaginal cancer, ovarian cancer, gastric cancer, breast cancer, bladder cancer, colon cancer, prostate cancer, pancreatic cancer, lung cancer, cervical cancer, epidermal cancer, prostate cancer, head or neck cancer. In certain preferred embodiments, the cancer is pancreatic cancer. In other embodiments, the cancer is colon cancer. In certain embodiments, the cancer is a solid tumor. In various such embodiments, the cancer may be relapsed or refractory. In certain embodiments, the cancers described above are resistant to treatment with a BTK inhibitor. In certain embodiments, the cancers described above are resistant to treatment with a BTK inhibitor as a monotherapy. In certain embodiments, the cancers are resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain preferred embodiments, the cancer is resistant to treatment with ibrutinib.

In other embodiments, the disease or disorder is an inflammatory disease or disorder. In certain embodiments, the inflammatory disease or disorder is an autoimmune disease or disorder. In certain embodiments, the inflammatory disease or disorder is an ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, autoimmune hematological disorders, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven- Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior or posterior),

Sjogren's syndrome, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis, idiopathic nephrotic syndrome, minimal change nephropathy, chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic urticarial dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma, acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, fibrositis, gastritis, gastroenteritis, nasal sinusitis, ocular allergy, silica induced diseases, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, juvenile rheumatoid arthritis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, urticaria, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angitis, urticarial, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute or chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS) and osteoarthritis. In certain preferred embodiments, the inflammatory disease or disorder is hypercytokinemia. In certain embodiments, the hypercytokinemia is induced by an infectious agent. In certain embodiments, the infectious agent is a virus. In certain preferred embodiments, the virus is a coronavirus (e.g., COVID-19). In other embodiments, the infectious agent is a bacteria. In certain embodiments, the inflammatory disease or disorder is graft vs host disease (GVHD). In certain embodiments, the GVHD is chronic graft vs host disease (cGVHD). In certain embodiments, the GVHD is sclerodermatous GVHD, steroid resistant GVHD,

cyclosporin-resistant GVHD, GVHD, oral GVHD, reticular oral GVHD, erosive GVHD, or ulcerative oral GVHD. In certain embodiments, the GVHD is sclerodermatous GVHD. In certain embodiments, the GVHD is oral GVHD. In certain embodiments, the GVHD is reticular oral GVHD. In certain embodiments, the GVHD is erosive GVHD. In certain embodiments, the GVHD is ulcerative oral GVHD. In certain embodiments, the GVHD is overlap chronic GVHD. In certain embodiments, the GVHD is classic chronic GVHD. In certain embodiments, the GVHD is steroid resistant GVHD. In certain embodiments, the GVHD is cyclosporin-resistant GVHD. In certain embodiments, the GVHD is refractory. In certain embodiments, the GVHD is relapsed.

In certain embodiments, the diseases or disorders described above are resistant to treatment with a BTK inhibitor alone. In certain embodiments, the diseases or disorders described above are resistant to treatment with a BTK inhibitor as a monotherapy. In certain embodiments, the diseases or disorders are resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain preferred embodiments, the diseases or disorders are resistant to treatment with ibrutinib.

In certain embodiments, the disease or disorder is associated with chronic anemia. In certain embodiments, the disease or disorder is chronic anemia. In certain embodiments, the disease or disorder is associated with transfusion dependency.

In certain embodiments, the subject is an adult human.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 50 mg orally once per day; and the disease or disorder is DLBCL. In certain embodiments, the DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 50 mg orally once per day; and the disease or disorder is FL. In certain embodiments, the FL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 300 mg orally once per day; and the disease or disorder is WM. In certain embodiments, the WM is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 50 mg orally twice per day; and the disease or disorder is DLBCL. In certain embodiments, the DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 300 mg orally twice per day; and the disease or disorder is LPL. In certain embodiments, the LPL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 300 mg orally twice per day; and the disease or disorder is GCB DLBCL. In certain embodiments, the GCB DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 400 mg orally twice per day; and the disease or disorder is ABC DLBCL. In certain embodiments, the ABC DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 400 mg orally twice per day; and the disease or disorder is MZL. In certain embodiments, the MZL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 300 mg orally twice per day; and the disease or disorder is MZL. In certain embodiments, the MZL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor is Compound 1; Compound 1 is administered at a dosage of about 300 mg orally twice per day; and the disease or disorder is MALT. In certain embodiments, the MALT is relapsed or refractory.

In certain embodiments, Compound 1 is administered continuously (*e.g.*, Compound 1 is administered without a drug holiday). In other embodiments, Compound 1 is administered intermittently (*e.g.*, Compound 1 is administered continuously interrupted by one or more drug holidays). In certain embodiments, each drug holiday lasts for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days. In certain preferred embodiments, a drug holiday lasts for 7 days. In further preferred embodiments, Compound 1 is administered daily for three weeks followed by a one-week drug holiday, optionally followed by three weeks of daily administration and a one-week drug holiday, which cycle may be further repeated. In certain embodiments, the aforementioned dosing regimen continues, alternating periods of administration with holidays, until a change of disease state is observed (*e.g.*, until a complete response, a partial response, or unacceptable toxicity is observed). Methods of treating certain diseases and disorders with Compound 1 are disclosed in PCT/U20S21/030192, the contents of which are fully incorporated by reference herein.

Prior Therapies

The methods disclosed herein may be used as a first line therapy or they may be applied to patients who have failed to achieve a response, either partial or full, using one or more previous anti-cancer therapies or anti-inflammatory therapies. In certain embodiments, the subject has previously received at least one anti-cancer therapy. In certain embodiments, the

patient has previously received one anti-cancer therapy. In other embodiments, the patient has previously received two anti-cancer therapies. In yet other embodiments, the patient has previously received three anti-cancer therapies. In yet other embodiments, the patient has previously received four anti-cancer therapies. In yet other embodiments, the patient has previously received five anti-cancer therapies. In certain embodiments, the at least one anti-cancer therapy is selected from an anti-CD20 antibody, a nitrogen mustard, a steroid, a purine analog, a DNA topoisomerase inhibitor, a DNA intercalator, a tubulin inhibitor, a BCL-2 inhibitor, a proteasome inhibitor, a toll-like receptor inhibitor, a kinase inhibitor, an SRC kinase inhibitor, a PI3K kinase inhibitor, BTK inhibitor, a glutaminase inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor and a methylating agent; or a combination thereof. In certain embodiments, the anti-cancer therapy is selected from ibrutinib, rituximab, bendamustine, bortezomib, dexamethasone, chlorambucil, cladribine, cyclophosphamide, doxorubicin, vincristine, venetoclax, ifosfamide, prednisone, oprozomib, ixazomib, acalabrutinib, zanubrutinib, IMO-08400, idelalisib, umbrelasib, CB-839, fludarabine, and thalidomide; or a combination thereof. In certain embodiments, the anti-cancer therapy is ibrutinib. In certain embodiments, the anti-cancer therapy is ibrutinib and rituximab. In certain embodiments, the anti-cancer therapy is bendamustine. In certain embodiments, the anti-cancer therapy is bendamustine and rituximab. In certain embodiments, the anti-cancer therapy is bortezomib. In certain embodiments, the anti-cancer therapy is bortezomib and dexamethasone. In certain embodiments, the anti-cancer therapy is bortezomib and rituximab. In certain embodiments, the anti-cancer therapy is bortezomib, rituximab, and dexamethasone. In certain embodiments, chlorambucil. In certain embodiments, the anti-cancer therapy is cladribine. In certain embodiments, the anti-cancer therapy is cladribine and rituximab. In certain embodiments, the anti-cancer therapy is cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (i.e., CHOP-R). In certain embodiments, the anti-cancer therapy is cyclophosphamide, prednisone, and rituximab (i.e., CPR). In certain embodiments, the anti-cancer therapy is fludarabine. In certain embodiments, the anti-cancer therapy is fludarabine and rituximab. In certain embodiments, the anti-cancer therapy is fludarabine, cyclophosphamide, and rituximab. In certain preferred embodiments, the anti-cancer therapy is rituximab. In certain preferred embodiments, the anti-cancer therapy comprises rituximab. In certain embodiments, the anti-cancer therapy is rituximab, cyclophosphamide, and dexamethasone (i.e., RCD). In certain embodiments, the anti-cancer therapy is thalidomide. In certain embodiments, the anti-cancer therapy is thalidomide and rituximab. In certain embodiments, the anti-cancer therapy is venetoclax. In certain embodiments, the anti-cancer therapy is cyclophosphamide, bortezomib, and

dexamethasone (i.e. R-CyBorD). In certain embodiments, the anti-cancer therapy is a hypomethylating agent. In certain embodiments, the subject has previously received at least 6 cycles of a hypomethylating agent. In certain embodiments, the anti-cancer therapy is a combination of any of the foregoing, for example the subject may first receive rituximab and then at a later date receive a combination of rituximab, cyclophosphamide, and dexamethasone (i.e., RCD).

In certain embodiments, the subject has previously received at least one anti-inflammatory therapy. In certain embodiments, the patient has previously received one anti-inflammatory therapy. In other embodiments, the patient has previously received two anti-inflammatory therapies. In yet other embodiments, the patient has previously received three anti-inflammatory therapies. In yet other embodiments, the patient has previously received four anti-inflammatory therapies. In certain embodiments, the anti-inflammatory is a steroid (e.g., corticosteroid). In certain embodiments, the anti-inflammatory therapy is hydrocortisone, cortisone, ethamethasone, prednisone, prednisolone, triamcinolone, dexamethasone, or fludrocortisone; or a combination thereof.

The subject may also have received or been prepared for other, non-chemotherapeutic treatments, such as surgery, radiation, or a bone marrow transplant. In certain embodiments, the subject has previously received etoposide chemo-mobilization therapy. In certain embodiments, the subject has previously received a bone marrow transplant. In certain embodiments, the subject has previously received a stem cell transplant. In certain embodiments, the subject has previously received an autologous cell transplant. In certain embodiments, the subject has previously received an allogenic stem cell transplant. In certain embodiments, the subject has previously received a hematopoietic cell transplantation. In certain embodiments, the subject has previously received carmustine, etoposide, cytarabine, and melphalan (i.e., BEAM conditioning). In certain embodiments, the subject has previously received re-induction therapy.

The subject may have also previously exhibited a favorable outcome to prior therapy only to require additional treatment at a later date. In certain embodiments, the subject has previously achieved a partial response. In certain embodiments, the subject has previously achieved a good partial response. In certain embodiments, the subject has previously achieved a complete response. In certain embodiments, the cancer is relapsed. In certain embodiments, the cancer is refractory.

The subject may also have preexisting or developed one or more genetic mutations that render the subjects cancer more or less resistant to therapy. In certain embodiments, the subject

has a mutation in RICTOR. In certain embodiments, the subject has a N1065S mutation in RICTOR. In certain preferred embodiments, the subject has a mutation in MYD88. In certain even further preferred embodiments, the subject has a L265P mutation in MYD88. In certain embodiments, the subject has a mutation in TET2. In certain embodiments, the subject does not have a mutation in CXCR4. In other embodiments, the subject has a mutation in CXCR4. In certain embodiments, the subject shows early progression. In certain embodiments, the subject has not previously received a BTK inhibitor.

In certain embodiments, following administration of the compound, the subject achieves a partial response. In certain embodiments, following administration of the compound, the subject achieves a good partial response. In other embodiments, following administration of the compound, the subject achieves a complete response. In certain embodiments, the subject achieves a partial response within 7 days of receiving the compound. In certain embodiments, the subject achieves a good partial response within 7 days of receiving the compound. In certain embodiments, the subject achieves a complete response within 7 days of receiving the compound. In certain embodiments, the subject's tumor volume is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In certain embodiments, the subject's tumor volume is reduced by 5%. In certain embodiments, the subject's tumor volume is reduced by 10%. In certain embodiments, the subject's tumor volume is reduced by 15%. In certain embodiments, the subject's tumor volume is reduced by 20%. In certain embodiments, the subject's tumor volume is reduced by 25%. In certain embodiments, the subject's tumor volume is reduced by 30%. In certain embodiments, the subject's tumor volume is reduced by 35%. In certain embodiments, the subject's tumor volume is reduced by 40%. In certain embodiments, the subject's tumor volume is reduced by 45%. In certain embodiments, the subject's tumor volume is reduced by 50%. In certain embodiments, the subject's tumor volume is reduced by 55%. In certain embodiments, the subject's tumor volume is reduced by 60%. In certain embodiments, the subject's tumor volume is reduced by 65%. In certain embodiments, the subject's tumor volume is reduced by 70%. In certain embodiments, the subject's tumor volume is reduced by 80%. In certain embodiments, the subject's tumor volume is reduced by 85%. In certain embodiments, the subject's tumor volume is reduced by 90%. In certain embodiments, the subject's tumor volume is reduced by 95%.

Methods of Performing Immunohistochemical Staining

In the certain embodiments of the methods of the present disclosure, the expression level of NF- κ B p-p50 in the sample can be determined by immunohistochemical staining. Methods of performing immunohistochemical staining are generally known by those of skill in the art. In brief, the tissue sample is contacted with a NF- κ B p-p50 or NF- κ B p-p65 specific antibody. After an incubation period, the tissue sample is contacted with a secondary antibody. The secondary antibody recognizes and binds to the first antibody. The secondary antibody may contain a conjugated activity (*e.g.*, an enzymatic activity) that is used to detect the presence of the secondary antibody, and thus the presence of the first antibody, and thus the presence of NF- κ B p-p50 or NF- κ B p-p65. Example conjugated activities can be any known to those skilled in the art to be useful for creating a detectable immunohistochemical signal. Suitable enzyme conjugates for the secondary antibody include, for example, horseradish peroxidase (HRP), alkaline phosphatase, glucose oxidase, and β -galactosidase; also contemplated are fluorescent probes, radioactive isotopes, chemiluminescent compounds, bioluminescent compounds, or combinations thereof.

In certain embodiments, the NF- κ B p-p50 or NF- κ B p-p65 specific antibody is a commercially available NF- κ B p-p50 antibody. In certain embodiments, the NF- κ B p-p50 or NF- κ B p-p65 specific antibody is a polyclonal antibody. In certain embodiments, the NF- κ B p-p50 or NF- κ B p-p65 specific antibody is a monoclonal antibody. In certain embodiments, the NF- κ B p-p50 or NF- κ B p-p65 specific antibody is a rabbit antibody. In certain embodiments, the NF- κ B p-p50 specific antibody is phospho-p50 NF- κ B (Ser337) (sc-271908) Ab from Santa Cruz Biotechnology. In certain embodiments, the NF- κ B p-p65 specific antibody is phospho-p65 NF- κ B (Ser536) (ab86299) Ab from Abcam. In certain embodiments, the NF- κ B p-p65 specific antibody is phospho-p65 NF- κ B (Ser276) (ab194726) Ab from Abcam.

In certain embodiments, the secondary antibody is commercially available. In certain embodiments, the secondary antibody is a Peroxidase labelled polymer conjugated to goat anti-rabbit immunoglobulins, such as that contained in EnVision+ System-HRP kit (DAKO, Carpinteria, CA).

In the methods of the present disclosure, after the level of expression of NF- κ B p-p50 or NF- κ B p-p65 in the tissue sample is determined, that level is compared to the expression level of NF- κ B p-p50 in a reference sample. In certain embodiments, the reference sample is of the same or comparable tissue type as the tissue sample, but is known to have normal

expression levels of NF- κ B p-p50 or NF- κ B p-p65 or no expression of NF- κ B p-p50 or NF- κ B p-p65. In certain embodiments, the reference sample is normal, or non-diseased tissue of the same tissue type as the tissue sample, but taken from an individual or group of individuals known to exhibit normal expression levels of NF- κ B p-p50 or NF- κ B p-p65 or no expression of NF- κ B p-p50 or NF- κ B p-p65. In certain embodiments, the reference sample is normal, or non-diseased tissue of the same or comparable tissue type as the tissue sample taken from the same individual as the tissue sample. In certain embodiments, the reference sample comprises a normal, or non-diseased sub-population of cells within the tissue sample. In certain embodiments, the reference sample is a plurality of cells or a tissue that does not exhibit the phenotype of elevated level of NF- κ B p-p50 or NF- κ B p-p65 expression.

An elevated expression level will have been detected when the NF- κ B p-p50 or NF- κ B p-p65 expression level in the tissue sample is higher than the NF- κ B p-p50 or NF- κ B p-p65 expression level in the reference sample. Positive expression of NF- κ B p-p50 or NF- κ B p-p65 can be defined as cytoplasmic and/or nuclear positive staining of more than 50% of cancer cells.

In the immunohistochemical staining method of the present disclosure, a biological sample is obtained. The biological sample may be any specimen of tissue or any collection of cells from a tissue. The biological sample may come from any animal or human being. In certain embodiments, the biological sample is from a human being. In other embodiments, the biological sample is from an animal.

In the immunohistochemical staining method of the present disclosure, the biological sample is contacted with a first antibody specific for NF- κ B p-p50 or NF- κ B p-p65 to give a primary antibody-contacted biological sample. The first antibody is specific for NF- κ B p-p50, meaning that the antibody selectively binds to NF- κ B p-p50 or NF- κ B p-p65. In certain embodiments, the first antibody is a polyclonal antibody. In certain embodiments, the first antibody is a monoclonal antibody. In certain embodiments, the first antibody is a rabbit polyclonal antibody. In certain embodiments, the first antibody is a rabbit monoclonal antibody.

In the immunohistochemical staining method of the present disclosure, the first antibody-contacted biological sample is contacted with a secondary antibody that is specific for the first antibody, wherein the secondary antibody also has a conjugated activity. The secondary antibody must bind selectively to the first antibody. The secondary antibody can be

from the same species as the first antibody, or from a different species than the first antibody. The secondary antibody can be a polyclonal antibody or a monoclonal antibody.

The secondary antibody also has a conjugated activity, which can be an enzymatic activity. In certain embodiments, the enzymatic activity is an inherent activity of the secondary antibody. In other embodiments, the enzymatic activity of the secondary antibody is provided by an enzyme that is conjugated to the antibody.

In certain embodiments, the enzymatic activity of the secondary antibody is peroxidase activity. In other embodiments, the enzymatic activity of the secondary antibody is alkaline phosphatase activity. Exemplary conjugated enzymatic activities can be any known to those skilled in the art to be useful for creating a detectable immunohistochemical signal, including, for example, horseradish peroxidase (HRP), alkaline phosphatase, glucose oxidase, and β -galactosidase. Other immunohistochemical signals are also contemplated, including, for example, fluorescent probes, radioactive isotopes, chemiluminescent compounds, bioluminescent compounds, or combinations thereof.

In the immunohistochemical staining method of the present disclosure, the product of contacting the first antibody-contacted biological sample with a secondary antibody is a biological sample to which is bound the first antibody, and wherein the secondary antibody is bound to the first antibody. In the methods of the present disclosure, this product is contacted with a chromogenic substrate for the enzymatic activity of the secondary antibody.

The chromogenic substrate for the enzymatic activity of the secondary antibody is a chemical compound that changes color upon being reacted with the enzymatic activity of the secondary antibody. In certain embodiments, the chromogenic substrate is diaminobenzidine (DAB). In other embodiments, the chromogenic substrate is 3-Amino-9-ethylcarbazole (AEC). In other embodiments, the chromogenic substrate is 5-bromo-4-chloro-3-indolyl phosphate/ tetranitroblue tetrazolium (BCIP/TNBT). In still other embodiments, the chromogenic substrate is Naphthol AS-MX phosphate+Fast Blue BB.

After treating the sample with the chromogenic substrate, the product is then counterstained for a period of time. Any counterstain that sufficiently contrasts the color of the chromogenic substrate may be used. A number of different counterstains are known to those skilled in the art, including, for example, methyl green and hematoxylin.

In certain embodiments, the product is then counterstained for up to 1 minute. In certain embodiments, the product is counterstained for up to 10 seconds.

In certain embodiments, the counterstain is hematoxylin. Methods of using hematoxylin are known to those skilled in the art. *See, e.g.* Godwin Avwioro, Histochemical

uses of Haematoxylin – A Review, JPCS Vol. 1, April-June 2011, 24-34. The concentration of hematoxylin generally ranges from about 1 g/L to about 2 g/L.

Pharmaceutical Compositions

The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In preferred embodiments, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as a lotion, cream, or ointment.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example,

which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

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 phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol

monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl

alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal,

subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By “therapeutically effective amount” is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher et al. (1996)

Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans; and other mammals such as equines, cattle, swine, sheep, cats, and dogs; poultry; and pets in general.

In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent.

The present disclosure includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, l-ascorbic acid, l-aspartic acid, benzenesulfonic acid, benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, d-glucoheptonic acid, d-gluconic acid,

d-glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, l-malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pantoic acid, phosphoric acid, propionic acid, L-pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, and undecylenic acid acid salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

The methods and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science", McGraw-Hill Medical, New York, N.Y.

(2000); Motulsky, "Intuitive Biostatistics", Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., "Developmental Biology, 6th ed.", Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein, unless otherwise defined herein, are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

The term "agent" is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, e.g., a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents whose structure is known, and those whose structure is not known. The ability of such agents to inhibit AR or promote AR degradation may render them suitable as "therapeutic agents" in the methods and compositions of this disclosure.

A "patient," "subject," or "individual" are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

"Treating" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "preventing" is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical

condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount.

“Administering” or “administration of” a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age and/or the physical condition of the subject and the chemical and biological properties of the compound or agent (e.g., solubility, digestibility, bioavailability, stability and toxicity). In certain embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion. In certain embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (e.g., the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

A “therapeutically effective amount” or a “therapeutically effective dose” of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by

administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, and the nature and extent of the condition being treated, such as cancer or MDS. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to the alkyl may be substituted as well as where the alkyl is not substituted.

It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skilled person in the art to result chemically stable compounds which can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, nitro, silyl, acyl, acyloxy, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OCO-CH₂-O-alkyl, -OP(O)(O-alkyl)₂ or -CH₂-OP(O)(O-alkyl)₂. Preferably, "optionally substituted" refers to the replacement of one to four hydrogen radicals in a given structure with the substituents mentioned above. More preferably, one to three hydrogen radicals are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

As used herein, the term "alkyl" refers to saturated aliphatic groups, including but not limited to C₁-C₁₀ straight-chain alkyl groups or C₁-C₁₀ branched-chain alkyl groups. Preferably, the "alkyl" group refers to C₁-C₆ straight-chain alkyl groups or C₁-C₆ branched-chain alkyl groups. Most preferably, the "alkyl" group refers to C₁-C₄ straight-chain alkyl groups or C₁-C₄ branched-chain alkyl groups. Examples of "alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The "alkyl" group may be optionally substituted.

The term “acyl” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term “acylamino” is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term “acyloxy” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term “alkoxy” refers to an alkyl group having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term “alkoxyalkyl” refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term “alkyl” refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁₋₃₀ for straight chains, C₃₋₃₀ for branched chains), and more preferably 20 or fewer.

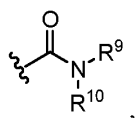
Moreover, the term “alkyl” as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted alkyl groups, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

The term “C_{x-y}” or “C_x-C_y”, when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. C₀alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. A C₁₋₆alkyl group, for example, contains from one to six carbon atoms in the chain.

The term “alkylamino”, as used herein, refers to an amino group substituted with at least one alkyl group.

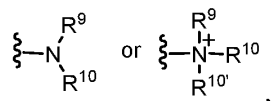
The term “alkylthio”, as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

The term “amide”, as used herein, refers to a group



wherein R^9 and R^{10} each independently represent a hydrogen or hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



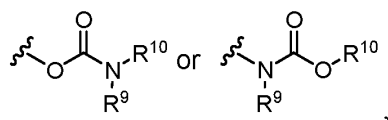
wherein R^9 , R^{10} , and $R^{10'}$ each independently represent a hydrogen or a hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term “aminoalkyl”, as used herein, refers to an alkyl group substituted with an amino group.

The term “aralkyl”, as used herein, refers to an alkyl group substituted with an aryl group.

The term “aryl” as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term “carbamate” is art-recognized and refers to a group



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl group.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbocycle” includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring

of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbonate” is art-recognized and refers to a group $-\text{OCO}_2-$.

The term “carboxy”, as used herein, refers to a group represented by the formula $-\text{CO}_2\text{H}$.

The term “cycloalkyl” includes substituted or unsubstituted non-aromatic single ring structures, preferably 4- to 8-membered rings, more preferably 4- to 6-membered rings. The term “cycloalkyl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is cycloalkyl and the substituent (e.g., R^{100}) is attached to the cycloalkyl ring, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, denzodioxane, tetrahydroquinoline, and the like.

The term “ester”, as used herein, refers to a group $-\text{C}(\text{O})\text{OR}^9$ wherein R^9 represents a hydrocarbyl group.

The term “ether”, as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include “alkoxyalkyl” groups, which may be represented by the general formula alkyl-O-alkyl.

The terms “halo” and “halogen” as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms “hetaralkyl” and “heteroaralkyl”, as used herein, refers to an alkyl group substituted with a hetaryl group.

The terms “heteroaryl” and “hetaryl” include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heteroaryl” and “hetaryl” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

The term “heteroatom” as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The term “heterocyclylalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle group.

The terms “heterocyclyl”, “heterocycle”, and “heterocyclic” refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heterocyclyl” and “heterocyclic” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term “hydrocarbyl”, as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and even trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

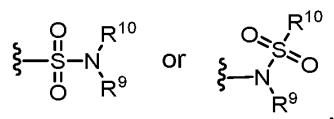
The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer atoms in the substituent, preferably six or fewer. A “lower alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

The term “sulfate” is art-recognized and refers to the group $-\text{OSO}_3\text{H}$, or a pharmaceutically acceptable salt thereof.

The term “sulfonamide” is art-recognized and refers to the group represented by the general formulae



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl.

The term “sulfoxide” is art-recognized and refers to the group $-\text{S}(\text{O})-$.

The term “sulfonate” is art-recognized and refers to the group SO_3H , or a pharmaceutically acceptable salt thereof.

The term “sulfone” is art-recognized and refers to the group $-\text{S}(\text{O})_2-$.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic

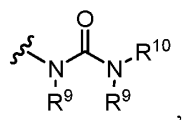
and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

The term “thioalkyl”, as used herein, refers to an alkyl group substituted with a thiol group.

The term “thioester”, as used herein, refers to a group $-C(O)SR^9$ or $-SC(O)R^9$ wherein R^9 represents a hydrocarbyl.

The term “thioether”, as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term “urea” is art-recognized and may be represented by the general formula



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl.

The term “modulate” as used herein includes the inhibition or suppression of a function or activity (such as cell proliferation) as well as the enhancement of a function or activity.

The phrase “pharmaceutically acceptable” is art-recognized. In certain embodiments, the term includes compositions, excipients, adjuvants, polymers and other materials 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.

“Pharmaceutically acceptable salt” or “salt” is used herein to refer to an acid addition salt or a basic addition salt which is suitable for or compatible with the treatment of patients.

The term “pharmaceutically acceptable acid addition salt” as used herein means any non-toxic organic or inorganic salt of any base compounds represented by Formula I.

Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono or di-acid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of Formula I are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, e.g., oxalates, may be used, for example, in the isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

The term “pharmaceutically acceptable basic addition salt” as used herein means any non-toxic organic or inorganic base addition salt of any acid compounds represented by Formula I or any of their intermediates. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium, or barium hydroxide. Illustrative organic bases which form suitable salts include aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline or ammonia. The selection of the appropriate salt will be known to a person skilled in the art.

Many of the compounds useful in the methods and compositions of this disclosure have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30. The disclosure contemplates all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds, salts, prodrugs or mixtures thereof (including all possible mixtures of stereoisomers). See, e.g., WO 01/062726.

Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the disclosure includes both mixture and separate individual isomers.

Some of the compounds may also exist in tautomeric forms. Such forms, although not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present disclosure.

“Prodrug” or “pharmaceutically acceptable prodrug” refers to a compound that is metabolized, for example hydrolyzed or oxidized, in the host after administration to form the compound of the present disclosure (e.g., compounds of formula I). Typical examples of prodrugs include compounds that have biologically labile or cleavable (protecting) groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Examples of prodrugs using ester or phosphoramidate as biologically labile or cleavable (protecting) groups are disclosed in U.S. Patents 6,875,751, 7,585,851, and 7,964,580, the disclosures of which are incorporated herein by reference. The prodrugs of this disclosure are metabolized to produce a compound of Formula I. The present disclosure includes within its scope, prodrugs of the compounds described herein. Conventional procedures for the selection and preparation of suitable prodrugs are described, for example, in “Design of Prodrugs” Ed. H. Bundgaard, Elsevier, 1985.

The phrase “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material useful for formulating a drug for medicinal or therapeutic use.

The term “Log of solubility”, “LogS” or “logS” as used herein is used in the art to quantify the aqueous solubility of a compound. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. A low solubility often goes along with a poor absorption. LogS value is a unit stripped logarithm (base 10) of the solubility measured in mol/liter.

As used herein, the phrase “expression level” refers to the level and or prevalence of expression of an expression product within a sample. For example, the expression level of a protein can be measured by staining a tissue sample (e.g., a plurality of cells) and measuring the prevalence (i.e., occurrence) and/or level of the protein across one or more cells (preferably a plurality of cells) of the tissue or across the tissue sample as a whole.

EXAMPLES

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1: Exemplary Method for Determining NF- κ B p-p50 or NF- κ B p-p65 Expression

Formalin-fixed, paraffin-embedded sections of human tonsil and lymphoma were used. Tissue sections (5 μ m) were deparaffinized, and antigen retrieval was carried out at 90-100°C in citrate buffer for 10-40 min. The sections were incubated in 1% hydrogen peroxidase for 10 minutes to quench endogenous tissue peroxidase. Tissue sections were then incubated with primary NF- κ B p-p50-specific antibody for 1 hour at room temperature. The primary NF- κ B p-p50-specific antibody used NF- κ B p-p50 (S337), sc-271908 from Santa Cruz Biotechnology.

The slides were stained using a standard EnVision+ System-HRP kit (DAKO, Carpinteria, CA) according to the manufacture's protocol. Immunohistochemical reactions were developed with diaminobenzidine as the chromogenic peroxidase substrate, and slides were counterstained with hematoxylin. Negative control samples included replacement of the primary antibody with nonimmune IgG1 (Dako).

Specific staining of the target molecule with low background staining was observed in human tonsil and lymphoma samples at 1:100 dilution of NF- κ B p-p50 Ab (Fig. 12C). Specifically, nuclear and/or cytoplasmic expression of NF-kappaB p-p50 was found in all 6 SD cases treated with 50 mg QD (2 cases, tumor regression), 50 mg BID (1 case), 200 BID (1 case, tumor regression) and 400 BID (2 cases). Expression of NF-kappaB p-p50 was not detected in 7 of 8 cases with PD including patients treated with 50 mg QD (1 case), 100 mg QD (1 case), 100 mg BID (3 cases), 200 mg BID (1 case) and 400 BID (1 case). Statistically significant correlation between expression of NF-kappaB p-p50 in tumor biopsy and SD in NHL patients treated with Compound 1 ($p < 0.05$) was observed. Analysis of NF-kappaB p-p50 expression in paired tumor biopsy samples (3 cases) collected before and after the treatment with Compound 1 revealed a significant downregulation of NF-kappaB p-p50 expression in tumors obtained from Compound 1-treated NHL patients. The in vitro experiments demonstrated that the expression of NF-kappaB p-p50 in 3D lymphoma organoids treated with clinically relevant concentration of Compound 1. Our results support further development of NF-kappaB p-p50 as a potential predictive and pharmacodynamic biomarker of IRAK4 inhibitors.

In summary, the expression of NF-kappaB p-p50 can serve as biomarker to predict SD in response to the treatment with an IRAK4 modifying compound in NHL patients. NF-kappaB p-p50 selection strategy might be used in future clinical trials to identify NHL patients which are most likely to respond to treatment with an IRAK4 modifying compound in combination with chemotherapy or targeted therapeutics.

Example 2: Performance of Compound 1 in WM

The patient is an otherwise healthy male who presented age 49 with complaints of severe fatigue. Routine labs were notable for an elevated erythrocyte sedimentation rate and anemia; therefore, he was referred to hematology/oncology. Further work-up revealed an IgM lambda m-protein on serum protein electrophoresis and a hypercellular bone marrow with trilineage hematopoiesis and an atypical lymphoplasmacytic infiltrate, consistent with WM. CT scans did not reveal lymphadenopathy or hepatosplenomegaly.

Due to symptomatic cytopenia and profound fatigue, treatment was recommended. The patient received rituximab induction 375 mg/m² IV weekly for 8 weeks then rituximab maintenance every 3 months for 8 doses between 2005 and 2007 achieving a very good partial remission. He did well for approximately 4 years at which time his disease progressed, and he developed recurrent symptomatic anemia as well as new grade 1 sensory peripheral neuropathy involving the hands and feet. He was retreated with rituximab between June and September of 2011 achieving stable disease with a numeric increase in IgM from 1476 to 2042 mg/dL during this time and no improvement in symptoms. Repeat bone marrow biopsy 11/2011 showed a 90% cellular marrow with WM accounting for 20% of cellularity, IgM lambda plasma cells accounting for 5-10% of cellularity, normal cytogenetics, no increase in reticulin staining, and trace stainable iron. CT scans at that time were without lymphadenopathy or organomegaly. By December 2012, his serum IgM had increased to 3380 mg/dL, IgM lambda m-protein was 2.37 g/dL. He was referred to a tertiary care center for further management where induction chemotherapy followed by autologous stem cell transplantation was recommended. In early 2013 he received 2 cycles of rituximab, cyclophosphamide, bortezomib, and dexamethasone (R-CyBorD) achieving partial remission (PR) with a decrease in IgM to 1285 mg/dL and m-protein to 0.88 g/dL. The patient then received rituximab, ifosfamide, etoposide chemo-mobilization and stem cell collection in 6/2013 after which his IgM and m-protein remained unchanged. Further cytoreduction with 2 cycles of bendamustine and rituximab (BR) was administered pre-transplant which deepened the patient's partial response (IgM 454 mg/dL, m-protein 0.30 g/dL). He then underwent autologous stem cell transplantation with BEAM conditioning (carmustine, etoposide, cytarabine, melphalan) in October 2013 without complication and achieved a very good partial response (VGPR) with IgM nadir post-transplant of 135 mg/dL and m-protein detectable by immunofixation only in 1/2014.

The patient remained asymptomatic for over 4 years with a slow increase in m-protein and IgM during that time. By mid-2017 he started to experience increased fatigue. Bone marrow evaluation 11/2017 revealed a normocellular marrow with 30% involvement by WM

and normal cytogenetics. Next generation sequencing revealed RICTOR N1065S mutation as well as MYD88 L265P mutation and TET2 mutation in a subclonal population. There was no evidence of CXCR4 genomic alteration. By late 2018 his fatigue had started to interfere with his ability to perform his usual activities, so treatment was again recommended. Several options were discussed including clinical trials and standard of care Bruton's tyrosine kinase inhibitor (BTKi) therapy. Given his clinical history, current symptoms, known mutational landscape, and personal preference he was enrolled in phase 1, dose-escalation study of the novel oral IRAK4 inhibitor, Compound 1, in patients with relapsed or refractory B-cell malignancies (NCT03328078).

Baseline testing in 12/2018 included a bone marrow biopsy showing 5-10% involvement by WM, m-protein of 1.66 g/dL, IgM 2,801 mg/dL, and a computed tomography scan without pathological lymphadenopathy or hepatosplenomegaly. Quantitative immunoglobulins and serum protein electrophoresis were obtained each cycle to determine response to treatment (FIG. 1).

The patient initiated treatment at the first dose level, 50mg. He tolerated therapy well without adverse events. During the first six 21-day cycles his m-protein slowly but steadily trended down to 1.55 g/dL and IgM initially increased from 2801 to 2866 mg/dL during the first 2 cycles then decreased to 2639 by cycle 6 day 1 (FIG. 1). Using a standard 3+3 design the subsequent dose level, 100mg po BID, was cleared per protocol. Considering evidence of response without noted toxicity, the patient was a candidate to escalate to 100mg po BID starting with cycle 7 day 1 in 4/2019. He had continued stable disease (SD) with down trending IgM and m-protein during cycles 7 and 8 without evidence of toxicity, and therefore became a candidate to escalate to the next cleared dose level of 200mg po BID starting with cycle 9 day 1 in 5/2019. Prior to 200mg BID dose escalation his baseline IgM was 2245 mg/dL and m-protein of 1.37 g/dL. His baseline symptom of fatigue was slightly improved but persistent. He continued to enjoy a seemingly dose-dependent reduction in tumor markers at the 200mg po BID dose level and by the summer of 2019 his fatigue had completely resolved. He reported a significant improvement in his quality of life with resolution of fatigue and returned to a rigorous daily exercise program that he had been unable to perform for the last 2 years due to WM-related symptoms. In 8/2019 he was noted to have an asymptomatic grade 2 creatine phosphokinase (CPK) elevation, extensive work-up and physical exam was unrevealing. He reduced the intensity of his exercise program and the asymptomatic CPK elevation resolved completely without need for Compound 1 dose delay or reduction. During cycles 15 through 20, while on the 200mg po BID dose, the patient's IgM plateaued around 1500 mg/dL and m-

protein plateaued near 0.9 g/dL. Based on evolving safety data at higher dose levels, the patient was escalated to 300g po BID starting with cycle 20 in 1/2020. He again experienced a seeming dose-dependent acceleration of response without noted toxicity and achieved PR as of C22 day 1 (m-protein 0.68 g/dL, IgM 1241 mg/dL). He remains on Compound 1 300mg po BID.

Therapies in WM involve targeting pathways associated with the known mutations of MYD88 and CXCR-4. Previous studies have shown the role of IRAK4 in signaling cascade involved in stimulatory effects of proinflammatory cytokines through forming a complex with MYD88. Thus, IRAK4 is an essential component in regulating immune responses and those with dysfunctions in either part of the complex can lead to immune deficiencies or immune dysregulation. With the addition of an IRAK4 inhibitor, a strong association is formed between IRAK4 and MYD88 and a weak association is formed with IRAK-1, thus reducing the ubiquitination of IRAK1 ultimately leading to decreased IL-1 induced signaling and cytokine production.

Through inhibition of IRAK4, Compound 1 prevents NF- κ B activation, leading to decreased inflammatory cytokine production and potential antineoplastic, immunomodulatory, and anti-inflammatory effects. Preclinical studies also suggest that Compound 1 affects TLR/IL1R signaling which may prevent the inflammatory process in auto-immune conditions.

This patient has well tolerated continuous oral treatment with Compound 1 for close to 18 months. His tumor burden has been shrinking in a dose-dependent manner, reaching partial response status (PR) according to the 6th International Workshop on WM response criteria (FIG. 1). The patient's quality of life improved from baseline with resolution of fatigue, even allowing him vigorous physical exercise that he had enjoyed prior to disease onset. However, this resulted in intermittent asymptomatic grade 2 elevation of CK which resolved with exercise moderation without the need of holding or reducing Compound 1 exposure.

Example 3: Performance of Compound 1 in DLBCL, FL, HGBL, WM, LPL, MZL, and MCL

Study Design and Methods

Phase I trial Compound 1 is a dose escalation trial with a 3 + 3 design. Seven dosing cohorts included 50 and 100 mg QD, and 50, 100, 200, 300, or 400 mg BID of daily continuous oral monotherapy in 21-Day cycles. Objective included safety and tolerance (primary), pk/pd and early efficacy (secondary), and biomarker correlations (exploratory). 31 patients with resistant or refractory, advanced NHL have been enrolled. Details of the patient population are set forth in Table 1 below.

Table 1- Summary of Adverse Effects

Characteristics & Disposition	Overall (N=31)
Male, n (%)	26 (80)
Female, n (%)	5 (16)
Age, median years (range)	69 (40-75)
Histology, n (%)	
Diffuse large B-cell lymphoma (DLBCL)	14 (45)
Transformed follicular lymphoma (t-FL/DLBCL) *	6 (19)
Waldenstrom's Macroglobulinemia (WM)	4 (13)
Other Lymphoma**	4 (13)
Prior Therapies	
No. prior regimens [Median (range)]	4 (1-8)
Ibrutinib inhibitor, n (%)	6 (19)
CAR-T, n (%)	5 (16)
ASCT	7(23)

*High grade composite low-high grade disease per local pathology report

**Includes Lymphoplasmacytic (n=2), mantle cell (n=2), marginal zone (n=2), high grade MYC-BCL₆ (n=1)

Results

Compound 1 was well tolerated. Eight patients were exposed at the highest dose level of 400 mg BID: 2 of 5 DLT-evaluable patients had Grade 3 rhabdomyolysis (DLTs), without complications and reversible after treatment interruption and hydration / analgesic treatment – both subsequently continued treatment at lower doses of 200 or 300 mg BID, respectively. Six patients have tolerated 300 mg BID well without DLT. Most non-hematologic TEAEs were Grade 1 or 2 and manageable, including diarrhea, vomiting, fatigue, dyspnea, and myalgia. Mild/moderate, neutropenia, anemia, thrombocytopenia; only 4 Grade 3 combined episodes in 18 patients at dose levels ranging between 200 and 400 mg BID without complications (Table 2). No toxic deaths. Pharmacokinetics has shown favorable characteristics with dose-proportional increases in exposure. Similar pharmacodynamic changes were shown in cytokine reductions. Treatment duration ranged between <1 and 18+ months with sustained disease control. Eight of 28 evaluable patients experienced overall tumor burden decreases of $\geq 20\%$ from baseline – more at higher doses (Table 4). A WM patient with sustained PR underwent intra-patient dose escalation and had a dose/response relationship and very good treatment

tolerance (FIG. 3). Downstream pharmacodynamic markers of IRAK4 and molecular characteristics including cell-of-origin will be presented.

Table 2- Summary of Adverse Effects

Adverse Reaction	200 mg BID (n=5)		300 mg BID (n=6) (%)		400 mg BID (n=8) (%)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Diarrhea	20	0	40	0	25	0
Nausea	20	0	17	0	50	0
Vomiting	20	0	20	20	25	0
Constipation	20	0	0	0	20	0
Upper respiratory infection	40	20	0	0	12.5	0
Cough	40	0	0	0	0	0
Myalgia	40	0	0	0	37.5	0
Fatigue	40	0	0	0	50	0
Oedema	25	0	0	0	0	0
Headache	20	0	0	0	12.5	0
Dizziness	0	0	0	0	25	0
Insomnia	20	0	0	0	12.5	0
Dyspnoe	20	0	0	0	12.5	12.5
Peripheral sensory neuropathy	0	0	0	0	25	0
Back pain	20	0	0	0	12.5	0
Muscle weakness	20	20	0	0	12.5	0
Rhabdomyolysis	0	0	0	0	25	25
Dehydration	20	0	0	0	12.5	0

Table 3- Summary of Adverse Hematological Effects

	Compound 1 200 mg BID N=5		Compound 1 300 mg BID N=6		Compound 1 400 mg BID N=8	
	All Grades n (%) [E]	Grade 3 or Higher n (%) [E]	All Grades n (%) [E]	Grade 3 or Higher n (%) [E]	All Grades n (%) [E]	Grade 3 or Higher n (%) [E]
Neutropenia	2 (40.0) [3]	2 (40.0) [2]	1 (16.7) [5]	1 (16.7) [1]	2 (25.0) [3]	0
Anemia	1 (20.0) [1]	0	2 (33.3) [3]	0	1 (12.5) [1]	1 (12.5) [1]
Thrombocytopenia	0	0	0	0	1 (12.5) [2]	1 (12.5) [2]

Table 4- Response Summary

NHL	Initial Dose	Final Dose	Tumor
Subtype	Level	Level	Reduction
DLBCL	50 mg qd	50 mg qd	24%
(transformed MZL)			
FL	50 mg qd	50 mg qd	35%
FL	100 mg qd	50 mg qd	49%
WM	50 mg bid	300 mg bid *	66% (PR)
DLBCL	50 mg bid	50 mg bid	11%
LPL	200 mg bid	300 mg bid *	20%
DLBCL-GCB	200 mg bid	300 mg bid	35%
DLBCL-ABC	400 mg bid	400 mg bid	42%
MZL	400 mg bid	400 mg bid	5%
MALT/MZL	400 mg bid	300 mg bid*	25%

In summary, Compound 1 demonstrated good safety and tolerance, desirable pharmacokinetic properties, and preliminary clinical activity.

Example 4: Performance of Compound 1 in AML and MDS***Study Design and Methods***

This is a single-arm dose escalation Phase 1 study of orally administered Compound 1 monotherapy in adult patients with AML or high risk MDS (NCT04278768). This study will be conducted in 2 parts: an initial dose escalation and dose expansion phase. The starting dose level is 200 mg BID which was determined to be safe, capable of achieving relevant levels of drug exposure as well as demonstrating signs of biologic activity and clinical efficacy in an NHL Study. Three patients with AML or MDS will be enrolled at the designated dose. If none of the first 3 patients experience a DLT during the first cycle, patients may be enrolled into the next higher dose level of 300 mg bid until a safe and effective RP2D is established.

This study is expected to enroll approximately 18 patients to establish the initial RP2D. The safety population will include all patients in the study who received any dose of Compound 1, and the efficacy population will include patients who have a valid baseline and post-baseline disease assessment and received at least one dose of the study drug. Each treatment cycle of Compound 1 will be 28 days in length and repeated in the absence of toxicity or disease progression.

The major study inclusion and exclusion criteria are as follows: Relapsed or refractory AML (primary or secondary, including treatment-related) after at least one standard treatment (including chemotherapy, re-induction therapy or stem cell transplantation) based on the assessment of the investigator or high/very high risk relapsed/refractory MDS (IPSS-R criteria), following at least 6 cycles of hypomethylating agents [HMA] or evidence of early progression. Patients diagnosed with acute promyelocytic leukemia (APL, M3), blast phase of CML, allogeneic hematopoietic stem cell transplant (Allo-HSCT) within 60 days of the first dose of Compound 1 or clinically significant graft-versus-host disease (GVHD) requiring ongoing up-titration of immunosuppressive medications prior to start of Compound 1 are excluded.

The primary objective is to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for Compound 1 in patients with AML and high risk MDS based on the safety and tolerability, DLTs and PK/PD findings.

Results

All initial patients completed cycle 1 with marrow blast reduction, including several marrow complete responses.

Cohort 1 (200 mg BID; cycle duration 4 weeks)

3 patients with hr-MDS; all with ongoing treatment (currently 2-4 cycles). No DLT 1st cycle. 1 dose reduction C2 for Gr. 3 dizziness.

Cohort 2 (300 mg BID)

4 patients (3 AML, 1 hr-MDS), all with ongoing treatment (currently 1-2 cycles). No DLT in first 3 patients).

Cohort 3 open (400 mg BID)

Open for enrollment.

Example 5: Performance of Compound 1 in Relapsed or Refractory Hematologic Malignancies

Study Design and Methods

This is a trial of orally administered Compound 1 in combination with ibrutinib in adult patients with relapsed or refractory hematologic malignancies. (NCT03328078). It has 2 parts: an initial dose escalation phase (Part A2) and an expansion part of 4 cohorts. In a 3x3 dose-escalation design, the starting oral dose of Compound 1 will be 200 mg BID, administered daily. Concurrently, patients receive ibrutinib daily at the labeled dose for the respective NHL subtype (560 mg or 420 mg). If well tolerated, the Compound 1 dose will be escalated to 300 mg BID. Objectives include safety/tolerance, pharmacokinetics, preliminary efficacy assessment, and exploratory biomarker correlations. Once the recommended Phase 2 dose (RP2D) for combination dose has been determined, the expansion phase (Part B) will assess efficacy (CR / ORR rate/duration), safety/tolerance, population PK, and biomarker correlations of the Compound 1 and ibrutinib combination. Part B will comprise four cohorts which includes: 1 – MZL, 2 – DLBCL, 3 – CNSL, and 4 – NHL with adaptive ibrutinib resistance (basket design).

Cohorts 1-3 must be BTK-inhibitor naïve. The latter population will have received and responded to ibrutinib monotherapy (no primary resistance). Once they have developed adaptive, secondary resistance and shown tumor progression, the combination of ibrutinib and Compound 1 will be given. (A brief gap of ibrutinib therapy of <3 weeks is acceptable.) This cohort will include patients with ibrutinib approved or NCCN recommended indications: MCL, MZL, CLL/SLL, WM/LPL, PCNSL (NCCN-listed).

Primary objective: Preliminary efficacy signal identification of improved objective responses in cohorts 1-3 compared to historical data, and demonstration of resistance reversal in cohort 4 for by showing objective responses after preceding progression.

The estimated sample size of up to approximately 18 patients in Part A2 is based on the standard 3+3 study design for dose escalation. The exact number of patients will be determined

by the number of cohorts required to establish the maximum tolerate dose (MTD) and Recommended Phase 2 Dose (RP2D) for Compound 1 when administered in combination with ibrutinib. For Part B dose expansion, up to 46 patients will be enrolled in each of 4 NHL cohorts. The safety population will include all patients in the study who received any dose of Compound 1 in combination with ibrutinib, and the efficacy population will include patients who have a valid baseline and post-baseline disease assessment and received at least one dose of the study combination drugs. Safety observations and measurements include drug exposure, AEs, safety laboratory tests, vital signs, physical examinations, ECGs, and ECOG performance status. Each treatment cycle of Compound 1 will be 21 days in length and repeated in the absence of toxicity or tumor progression and ibrutinib will be dose as per the label.

The major study inclusion and exclusion criteria for Part A2 of the combination therapy dose escalation are as follows: Diagnosis of histopathologically confirmed B-cell NHL, as per the WHO 2016 classification. Eligible NHL subtypes include follicular lymphoma, MZL, mantle cell lymphoma, DLBCL (including extranodal lymphomas of leg-, testicular-, or NOS type), CLL/SLL, primary or secondary CNS lymphoma and Waldenström macroglobulinemia / LPL. Patients with mantle cell lymphoma, MZL, WM/LPL, or CLL/SLL should meet clinical criteria for requiring treatment of their disease. Patients with the presence of an acute or chronic toxicity resulting from prior anti-cancer therapy, with the exception of alopecia, that has not resolved to Grade ≤ 1 , as determined by NCI CTCAE v 4.03 within 7 days prior to start of study will be excluded.

The study treatment, endpoints are to determine the safety and tolerability, DLTs, MTD, and RP2D of oral Compound 1 in combination with ibrutinib, with secondary endpoints to assess objective response rate, (ORR), duration response rate (DOR) DCR, PFS, and OS following treatment with Compound 1 in combination with ibrutinib.

Example 6: Performance of Compound 1 in Autoimmune Disorders

A subject suffering from an autoimmune condition (e.g., graft vs host disease) will be administered Compound 1 in a dose escalation study starting at 50 mg. The efficacy of Compound 1 will be determined by methods known to one of ordinary skill in the art.

Example 7: Exemplary treatment of OCL-LY10 and TF-1 cells with Compound 1

OCL-LY10 and TF-1 cells were treated with different concentration of Compound 1 at 3 μ M and 10 μ M. At 48 h post-treatment, cell lysates were obtained. Protein sample concentration was quantified and equal amount 20 μ g of whole protein extract was loaded in each well of SDS-polyacrylamide gel. Cell extracts were separated by 10% SDS-PAGE,

transferred to nitrocellulose membrane, and probed as indicated. The following antibodies were used for immunoblot analysis: NF-kB p-p50 S337 (Santa Cruz Biotechnology) and b-actin (Cell Signaling Technology). Expression of NF-kB p-p50 S337 was downregulated in Compound 1 treated OCL-Ly10 and TF-1 cell lines.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

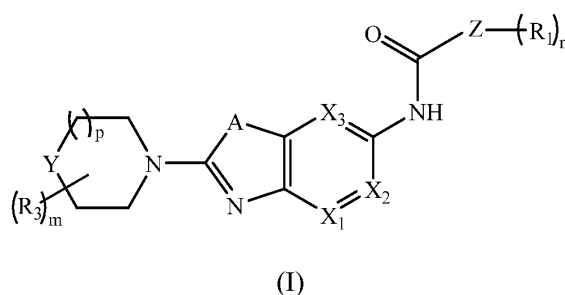
EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We claim:

1. A method of treating a disease or disorder in a subject, comprising:
obtaining a biological sample from the subject;
measuring an expression level of a phosphorylated NF- κ B in the biological sample;
comparing the level of expression of the phosphorylated NF- κ B to a reference level of
expression of phosphorylated NF- κ B; and
administering an IRAK4-modifying compound selected from an IRAK4 inhibitor or an
IRAK4 degrader to the subject if the expression of a phosphorylated NF- κ B is
elevated in the sample as compared to the reference level of expression of
phosphorylated NF- κ B.
2. A method of treating an IRAK4-mediated disease or disorder in a subject, comprising:
obtaining a biological sample from the subject;
measuring an expression level of a phosphorylated NF- κ B in the biological sample;
comparing the level of expression of the phosphorylated NF- κ B to a reference level of
expression of phosphorylated NF- κ B; and
administering an IRAK4-modifying compound selected from an IRAK4 inhibitor or an
IRAK4 degrader to the subject if the expression of a phosphorylated NF- κ B is
elevated as compared to the reference level of expression of phosphorylated NF- κ B.
3. The method of claim 1 or 2, wherein the reference level is a value obtained from a
subject or a plurality of subjects that does not suffer from the disease or disorder.
4. The method of claim 3, wherein the value is obtained from the same biological source
(e.g., tissue, blood, or other bodily fluid) as the biological sample.
5. The method of claim 3 or 4, wherein the value is obtained from tissue or blood.
6. The method of any one of claims 1-5, wherein the phosphorylated NF- κ B is NF- κ B p-
p50.

7. The method of claim 6, wherein the method comprises administering the IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression level of NF- κ B p-p50 is elevated in the sample.
8. The method of any one of claims 1-7, wherein the expression of NF- κ B p-p50 is nuclear expression.
9. The method of any one of claims 1-7, wherein the expression of NF- κ B p-p50 is cytoplasmic expression.
10. The method of any one of claims 1-7, wherein the expression of NF- κ B p-p50 is the combination of nuclear expression and cytoplasmic expression.
11. The method of any one of claims 1-5, wherein the phosphorylated NF- κ B is NF- κ B p-p65.
12. The method of claim 11, wherein the method comprises administering the IRAK4 inhibitor or an IRAK4 degrader to the subject if the expression level of NF- κ B p-p65 is elevated in the sample.
13. The method of claim 11 or 12, wherein the expression of NF- κ B p-p65 is nuclear expression.
14. The method of claim 11 or 12, wherein the expression of NF- κ B p-p65 is cytoplasmic expression.
15. The method of any one of claims 1-5, wherein the expression of NF- κ B p-p65 is the combination of nuclear expression and cytoplasmic expression.
16. The method of any one of claims 1-15, wherein the IRAK4-modifying compound is an IRAK4 inhibitor.
17. The method of any one of claims 1-16, wherein the IRAK4 inhibitor is represented by formula I:



or a pharmaceutically acceptable salt thereof;

wherein

X₁ and X₃ independently are CH or N; X₂ is CR₂ or N; provided one and not more than one of

X₁, X₂ or X₃ is N;

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or -NR_aR_b;

R₂ is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or -NR_aR_b; wherein the substituent is alkyl, amino, halo or hydroxyl;

R₃, at each occurrence, is alkyl or hydroxyl;

R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

'm' and 'n' are independently 0, 1 or 2; and

'p' is 0 or 1.

18. The method of claim 17, wherein

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b;

'm' is 0; and

'n' is 1.

19. The method of claim 17, wherein

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

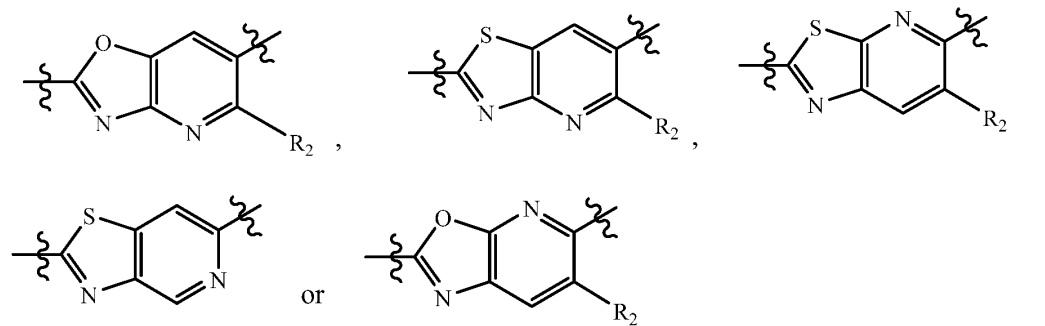
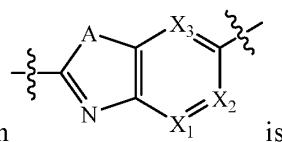
R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl;

'm' and 'n' are independently 0, 1 or 2; and

'p' is 0 or 1.

20. The method of any one of claims 17-19, wherein

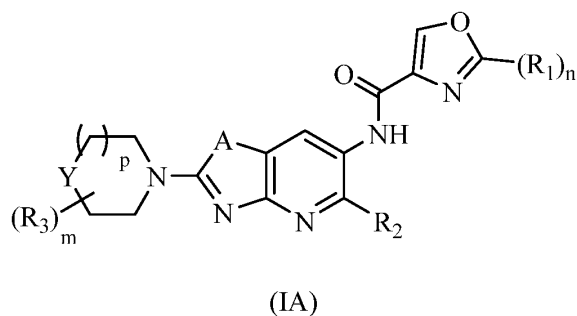


21. The method of any one of claims 17-20, wherein Z is aryl or 5- or 6-membered heterocyclyl.

22. The method of any one of claims 17-21, wherein Z is an optionally substituted heterocyclyl selected from phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl and

azabicyclo[3.2.1]octanyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; and R_a and R_b are independently hydrogen, alkyl or acyl.

23. The method of claim 17, wherein the IRAK4 inhibitor is represented by formula (IA):



or a pharmaceutically acceptable salt thereof..

24. The method of claim 23, wherein

A is O or S;

Y is -CH₂- or O;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b;

'm' is 0; and

'n' is 1.

25. The method of claim 23, wherein

A is O or S;

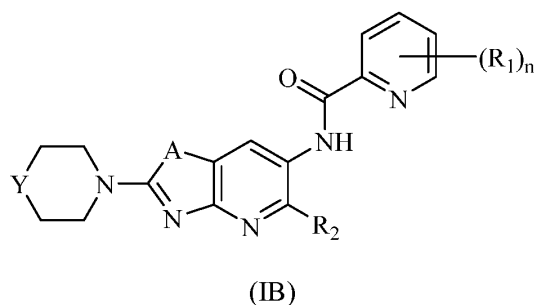
Y is -CH₂- or O;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

'm' and 'n' are independently 0, 1 or 2.

26. The method of claim 17, wherein the IRAK4 inhibitor is represented by formula (IB):



or a pharmaceutically acceptable salt thereof.

27. The method of claim 26, wherein

A is O or S;

Y is -CH₂- or O;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; and

'n' is 1.

28. The method of claim 26, wherein

A is O or S;

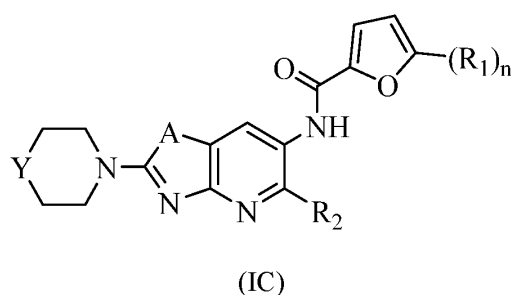
Y is -CH₂- or O;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

'm' and 'n' are independently 0, 1 or 2.

29. The method according to claim 17, wherein the compound of formula (I) is a compound of formula (IC)



or a pharmaceutically acceptable salt thereof.

30. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$; and R_a and R_b are independently hydrogen or acyl.

31. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, aminoalkyl, halo, or $-NR_aR_b$; and R_a and R_b are independently hydrogen or acyl.

32. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; and the substituent is alkyl, aminoalkyl, halo, or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.

33. The method of any one of claims 17-29, wherein R_1 is optionally substituted heterocyclyl; and the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.

34. The method of any one of claims 17-33, wherein R_1 is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl.

35. The method of any one of claims 17-29, wherein R_1 is optionally substituted pyrazolyl, wherein the substituent is alkyl, hydroxyl or $-NR_aR_b$.

36. The method of any one of claims 35-29, wherein R_1 is halo.

37. The method of any one of claims 17-36, wherein R_2 is hydrogen, cycloalkyl, heterocyclyl or $-NR_aR_b$.

38. The method of any one of claims 17-36, wherein R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl.
39. The method of any one of claims 17-36, wherein R₂ is optionally substituted heterocyclyl selected from piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidiny, pyrazolyl, furanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is hydroxyl, halo, alkyl or amino.
40. The method of any one of claims 17-39, wherein R₂ is piperidinyl, pyrrolidinyl, morpholinyl, or piperazinyl.
41. The method of any one of claims 17-36, wherein R₂ is hydrogen.
42. The method of any one of claims 17-36, wherein R₂ is cycloalkyl.
43. The method of claim 42, wherein R₂ is cyclopropyl.
44. The method of any one of claims 17-43, wherein R₃ is alkyl.
45. The method of any one of claims 17-44, wherein m is 0 and p is 1.
46. The method of any one of claims 17-44, wherein m is 0 or 2, and p is 0 or 1.
47. The method of any one of claims 17-46, wherein the IRAK4 inhibitor is selected from:
6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide hydrochloride;
N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-chloro-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide;

2-(2-chloropyridin-4-yl)-N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(2-morpholinothiazolo[4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;

2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-dimorpholinoxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-methylpiperazin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(3-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methylpyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide hydrochloride;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide hydrochloride;

N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methoxypyridin-4-yl)oxazole-4-carboxamide;

2-(6-methoxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;

N-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-aminopyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;

N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-acetamidopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

5-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)furan-3-carboxamide hydrochloride;

2-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

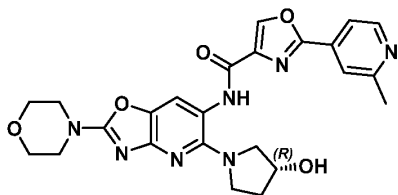
2-(2-aminopyridin-4-yl)-N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

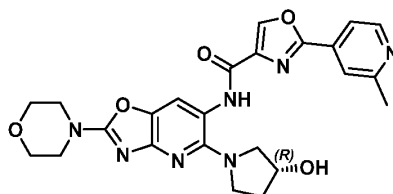
N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride; and
 N-(5-(2-hydroxypyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
 or a pharmaceutically acceptable salt or a stereoisomer thereof.

48. The method of any one of claims 1-16, wherein the IRAK4 inhibitor is



49. The method of any one of claims 1-16, wherein the IRAK4 inhibitor is a



pharmaceutically acceptable salt of

50. The method of claim 48 or 49, comprising administering 100 – 400 mg of the IRAK4 inhibitor to the subject twice per day.

51. The method of claim 48 or 49, comprising administering 200 – 400 mg of the IRAK4 inhibitor to the subject twice per day.

52. The method of claim 48 or 49, comprising administering 250 – 350 mg of the IRAK4 inhibitor to the subject twice per day.

53. The method of claim 48 or 49, comprising administering about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor to the subject twice per day.

54. The method of claim 48 or 49, comprising administering about 50 mg, about 75 mg, about 100 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, or about 400 mg of the IRAK4 inhibitor to the subject twice per day.
55. The method of claim 48 or 49, comprising administering about 50 mg, about 100 mg, about 200 mg, or about 300 mg of the IRAK4 inhibitor to the subject twice per day.
56. The method of claim 48 or 49, comprising administering about 200 mg of the IRAK4 inhibitor to the subject twice per day.
57. The method of claim 48 or 49, comprising administering about 225 mg of the IRAK4 inhibitor to the subject twice per day.
58. The method of claim 48 or 49, comprising administering about 250 mg of the IRAK4 inhibitor to the subject twice per day.
59. The method of claim 48 or 49, comprising administering about 275 mg of the IRAK4 inhibitor to the subject twice per day.
60. The method of claim 48 or 49, comprising administering about 300 mg of the IRAK4 inhibitor to the subject twice per day.
61. The method of claim 48 or 49, comprising administering about 325 mg of the IRAK4 inhibitor to the subject twice per day.
62. The method of claim 48 or 49, comprising administering about 350 mg of the IRAK4 inhibitor to the subject twice per day.
63. The method of claim 48 or 49, comprising administering about 375 mg of the IRAK4 inhibitor to the subject twice per day.
64. The method of claim 48 or 49, comprising administering about 400 mg of the IRAK4 inhibitor to the subject twice per day.

65. The method of claim 48 or 49, comprising administering about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor to the subject once per day.
66. The method of claim 48 or 49, comprising administering about 50 mg of the IRAK4 inhibitor to the subject once per day.
67. The method of claim 48 or 49, comprising administering about 75 mg of the IRAK4 inhibitor to the subject once per day.
68. The method of claim 48 or 49, comprising administering about 100 mg of the IRAK4 inhibitor to the subject once per day.
69. The method of claim 48 or 49, comprising administering about 125 mg of the IRAK4 inhibitor to the subject once per day.
70. The method of claim 48 or 49, comprising administering about 150 mg of the IRAK4 inhibitor to the subject once per day.
71. The method of any one of claims 1-70, wherein the IRAK4 inhibitor or IRAK4 degrader is orally administered to the subject.
72. The method of claim 48 or 49, comprising orally administering about 200 mg of the IRAK4 inhibitor to the subject twice per day.
73. The method of claim 48 or 49, comprising orally administering about 225 mg of the IRAK4 inhibitor to the subject twice per day.
74. The method of claim 48 or 49, comprising orally administering about 250 mg of the IRAK4 inhibitor to the subject twice per day.
75. The method of claim 48 or 49, comprising orally administering about 275 mg of the IRAK4 inhibitor to the subject twice per day.

76. The method of claim 48 or 49, comprising orally administering about 300 mg of the IRAK4 inhibitor to the subject twice per day.
77. The method of claim 48 or 49, comprising orally administering about 325 mg of the IRAK4 inhibitor to the subject twice per day.
78. The method of claim 48 or 49, comprising orally administering about 350 mg of the IRAK4 inhibitor to the subject twice per day.
79. The method of claim 48 or 49, comprising orally administering about 375 mg of the IRAK4 inhibitor to the subject twice per day.
80. The method of claim 48 or 49, comprising orally administering about 400 mg of the IRAK4 inhibitor to the subject twice per day.
81. The method of claim 48 or 49, comprising administering about 50 mg of the IRAK4 inhibitor to the subject once per day.
82. The method of claim 48 or 49, comprising administering about 75 mg of the IRAK4 inhibitor to the subject once per day.
83. The method of claim 48 or 49, comprising administering about 100 mg of the IRAK4 inhibitor to the subject once per day.
84. The method of claim 48 or 49, comprising administering about 125 mg of the IRAK4 inhibitor to the subject once per day.
85. The method of claim 48 or 49, comprising administering about 150 mg of the IRAK4 inhibitor to the subject once per day.
86. The method of any one of claims 1-16, wherein the IRAK4-modifying compound is PF-06650833 or BAY 1830839.
87. The method of any one of claims 1-16, wherein the IRAK4-modifying compound is an IRAK4 degrader.

88. The method of claim 87, wherein the IRAK4 degrader is KT-474.
89. The method of any one of claims 1-88, wherein the method further comprises conjointly administering a BCL-2 inhibitor to the subject.
90. The method of claim 89, wherein the BCL-2 inhibitor is venetoclax.
91. The method of claim 89, comprising administering 400 mg of venetoclax daily.
92. The method of claim any one of claims 90, wherein the venetoclax is administered orally.
93. The method of claim 89, comprising orally administering 400 mg of venetoclax daily.
94. The method of any one of claims 1-88, wherein the method further comprises conjointly administering a BTK inhibitor to the subject.
95. The method of claim 94, wherein the BTK inhibitor is ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224.
96. The method of claims 94, wherein the BTK inhibitor is acalabrutinib.
97. The method of claim 96, comprising administering 200 mg of acalabrutinib daily.
98. The method claim 96, wherein the acalabrutinib is administered orally.
99. The method of claim 96, comprising orally administering 200 mg of acalabrutinib daily.
100. The method of claim 94, wherein the BTK inhibitor is ibrutinib.
101. The method of claim 100, comprising administering 420 mg of ibrutinib daily.
102. The method of claim 100, comprising administering 560 mg of ibrutinib daily.
103. The method of claim 100, wherein the ibrutinib is administered orally.

104. The method of claim 11, comprising orally administering 420 mg of ibrutinib daily.
105. The method of claim 100, comprising orally administering 560 mg of ibrutinib daily.
106. The method of claims 96, wherein the BTK inhibitor is zanubrutinib.
107. The method of claim 106, comprising administering 160 mg of zanubrutinib twice daily.
108. The method of claim 106, comprising administering 320 mg of zanubrutinib once daily.
109. The method of claim 96, wherein the zanubrutinib is administered orally.
110. The method of claim 106, comprising orally administering 160 mg of zanubrutinib twice daily.
111. The method of claim 106, comprising orally administering 320 mg of zanubrutinib once daily.
112. The method of any one of claims 1-111, wherein the disease or disorder is a cancer.
113. The method of any one of claims 1-112, wherein the disease or disorder is a hematological malignancy.
114. The method of claim 113, wherein the hematological malignancy is a non-Hodgkin's lymphoma.
115. The method of claim 113, wherein the hematological malignancy is a leukemia or lymphoma.
116. The method of any one of claims 113-115, wherein the is hematological malignancy is myelogenous leukemia, myeloid leukemia (e.g., acute myeloid leukemia), myelodysplastic syndrome, lymphoblastic leukemia (e.g., acute lymphoblastic leukemia), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, follicular lymphoma,

diffuse large B-cell lymphoma (DLBCL) (e.g., DLBCL or ABC-DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, marginal zone lymphoma (MZL), Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, extranodal marginal zone B cell lymphoma, transformed high grade B-cell lymphoma (HGBL), lymphoplasmacytic lymphoma (LPL), central nervous system lymphoma (CNSL), or MALT lymphoma.

117. The method of claim 113, wherein the hematological malignancy is myelogenous leukemia.

118. The method of claim 113, wherein the hematological malignancy is myeloid leukemia (e.g., acute myeloid leukemia).

119. The method of claim 113, wherein the hematological malignancy is acute myeloid leukemia (e.g., AML).

120. The method of claim 119, wherein the AML is primary AML.

121. The method of claim 119, wherein the AML is secondary AML.

122. The method of any one of claims 119-121, wherein the AML is treatment related AML.

123. The method of claim 113, wherein the hematological malignancy is myelodysplastic syndrome.

124. The method of claim 123, wherein the myelodysplastic syndrome is high grade.

125. The method of claim 123, wherein the myelodysplastic syndrome is low grade.

126. The method of any one of claims 123-125, wherein the myelodysplastic syndrome is high risk.

127. The method of claim 113, wherein the hematological malignancy is lymphoblastic leukemia (e.g., acute lymphoblastic leukemia).

128. The method of claim 113, wherein the hematological malignancy is chronic lymphocytic leukemia (CLL).
129. The method of claim 128, wherein the CLL is high risk CLL.
130. The method of claim 113, wherein the hematological malignancy is small lymphocytic lymphoma (SLL).
131. The method of claim 113, wherein the hematological malignancy is follicular lymphoma.
132. The method of claim 113, wherein the hematological malignancy is diffuse large B-cell lymphoma (DLBCL).
133. The method of claim 113, wherein the hematological malignancy is activated B cell-like (ABC) DLBCL.
134. The method of claim 113, wherein the hematological malignancy is germinal center B cell-like (GCB) DLBCL.
135. The method of any one of claims 132-134, wherein the DLBCL is extranodal.
136. The method of any one of claims 132-135, wherein the DLBCL is extranodal leg lymphoma, extranodal testicle lymphoma, or extra nodal not otherwise specified (NOS) type lymphoma.
137. The method of claim 113, wherein the hematological malignancy is mantle cell lymphoma.
138. The method of claim 113, wherein the hematological malignancy is Waldenstrom's macroglobulinemia.
139. The method of claim 113, wherein the hematological malignancy is multiple myeloma.

140. The method of claim 113, wherein the hematological malignancy is marginal zone lymphoma.
141. The method of claim 113, wherein the hematological malignancy is Burkitt's lymphoma.
142. The method of claim 113, wherein the hematological malignancy is non-Burkitt high grade B cell lymphoma.
143. The method of claim 113, wherein the hematological malignancy is extranodal marginal zone B cell lymphoma.
144. The method of claim 113, wherein the hematological malignancy is transformed high grade B-cell lymphoma (HGBL).
145. The method of claim 113, wherein the hematological malignancy is lymphoplasmacytic lymphoma (LPL).
146. The method of claim 113, wherein the hematological malignancy is CNS lymphoma.
147. The method of claim 146, wherein the CNS lymphoma is primary CNS lymphoma (PCNSL).
148. The method of claim 113, wherein the hematological malignancy is MALT lymphoma.
149. The method of any one of claims 113-148, wherein the hematological malignancy is relapsed.
150. The method of any one of claims 113-149, wherein the hematological malignancy is refractory.
151. The method of claim 112, wherein the cancer is selected from brain cancer, kidney cancer, liver cancer, stomach cancer, penile cancer, vaginal cancer, ovarian cancer, gastric

cancer, breast cancer, bladder cancer, colon cancer, prostate cancer, pancreatic cancer, lung cancer, cervical cancer, epidermal cancer, prostate cancer, head or neck cancer.

152. The method of claim 112, wherein the cancer is pancreatic cancer.

153. The method of claim 112, wherein the cancer is colon cancer.

154. The method of any one of claims 151-153, wherein the cancer is a solid tumor.

155. The method of any one of claims 151-154, wherein the cancer is relapsed.

156. The method of any one of claims 151-155, wherein the cancer is refractory.

157. The method of any one of claims 1-156, wherein the disease or disorder is resistant to treatment with a BTK inhibitor.

158. The method of claim 157, wherein the disease or disorder is resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224.

159. The method of claim 157, wherein the disease or disorder is resistant to treatment with ibrutinib.

160. The method of claim 157, wherein the disease or disorder is resistant to treatment with acalabrutinib.

161. The method of any one of claims 1-111, wherein the disease or disorder is an inflammatory disease or disorder.

162. The method of claim 161, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.

163. The method of claim 161, wherein the inflammatory disease or disorder is an ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, autoimmune hematological disorders, hemolytic anemia, aplastic anemia, pure red cell

anemia, idiopathic thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven- Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior or posterior), Sjogren's syndrome, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis, idiopathic nephrotic syndrome, minimal change nephropathy, chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic urticarial dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma, acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, fibrositis, gastritis, gastroenteritis, nasal sinusitis, ocular allergy, silica induced diseases, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, juvenile rheumatoid arthritis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, urticaria, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticarial, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute or chronic gout, chronic gouty arthritis, psoriasis,

psoriatic arthritis, rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS) and osteoarthritis.

164. The method of claim 161, wherein the inflammatory disease or disorder is hypercytokinemia.

165. The method of claim 164, wherein the hypercytokinemia is induced by an infectious agent.

166. The method of claim 165, wherein the infectious agent is a virus.

167. The method of claim 166, wherein the virus is a coronavirus (e.g., COVID-19).

168. The method of claim 165, wherein the infectious agent is a bacteria.

169. The method of claim 161, wherein the inflammatory disease or disorder is graft vs host disease (GVHD).

170. The method of claim 161, wherein the GVHD is chronic graft vs host disease (cGVHD).

171. The method of claim 161, wherein the GVHD is sclerodermatous GVHD, steroid resistant GVHD, cyclosporin-resistant GVHD, GVHD, oral GVHD, reticular oral GVHD, erosive GVHD, or ulcerative oral GVHD.

172. The method of claim 170 or 171, wherein the GVHD is sclerodermatous GVHD.

173. The method of claim 170 or 171, wherein the GVHD is oral GVHD.

174. The method of claim 170 or 171, wherein the GVHD is reticular oral GVHD.

175. The method of claim 170 or 171, wherein the GVHD is erosive GVHD.

176. The method of claim 170 or 171, wherein the GVHD is ulcerative oral GVHD.

177. The method of any one of claims 170-176, wherein the GVHD is overlap chronic GVHD.
178. The method of any one of claims 170-176, wherein the GVHD is classic chronic GVHD.
179. The method of any one of claims 170-178, wherein the GVHD is steroid resistant GVHD.
180. The method of any one of claims 170-179, wherein the GVHD is cyclosporin-resistant GVHD.
181. The method of any one of claims 170-180, wherein the GVHD is refractory.
182. The method of any one of claims 170-181, wherein the GVHD is relapsed.
183. The method of any one of claims 1-182, wherein the disease or disorder is associated with chronic anemia.
184. The method of any one of claims 1-111, wherein the disease or disorder is chronic anemia.
185. The method of any one of claims 1-184, wherein the disease or disorder is associated with transfusion dependency.
186. The method of any one of claims 1-185, wherein the subject is an adult human.
187. The method of any one of claims 1-186, wherein the subject has previously received at least one anti-cancer therapy (e.g., an anti-cancer therapy or an anti-inflammatory therapy).
188. The method of claim 187, wherein the subject has previously received one anti-cancer therapy.
189. The method of claim 187, wherein the subject has previously received two anti-cancer therapies.

190. The method of claim 187, wherein the subject has previously received three anti-cancer therapies.
191. The method of claim 187, wherein the subject has previously received four anti-cancer therapies.
192. The method of claim 187, wherein the subject has previously received five anti-cancer therapies.
193. The method of any one of claims 187-192, wherein the at least one anti-cancer therapy is selected from an anti-CD20 antibody, a nitrogen mustard, a steroid, a purine analog, a DNA topoisomerase inhibitor, a DNA intercalator, a tubulin inhibitor, a BCL-2 inhibitor, a proteasome inhibitor, a toll-like receptor inhibitor, a kinase inhibitor, an SRC kinase inhibitor, a PI3K kinase inhibitor, BTK inhibitor, a glutaminase inhibitor, a steroid, a PD-1 inhibitor, a PD-L1 inhibitor, and a methylating agent; or a combination thereof.
194. The method of any one of claims 187-193, wherein the anti-cancer therapy is selected from ibrutinib, rituximab, bendamustine, bortezomib, dexamethasone, chlorambucil, cladribine, cyclophosphamide, doxorubicin, vincristine, venetoclax, ifosfamide, prednisone, oprozomib, ixazomib, acalabrutinib, zanubrutinib, IMO-08400, idelalisib, umbrelasib, CB-839, fludarabine, and thalidomide; or a combination thereof.
195. The method of any one of claims 187-194, wherein the therapy is dexamethasone.
196. The method of any one of claims 187-194, wherein the anti-cancer therapy is ibrutinib.
197. The method of any one of claims 187-194, wherein the anti-cancer therapy is ibrutinib and rituximab.
198. The method of any one of claims 187-194, wherein the anti-cancer therapy is bendamustine.
199. The method of any one of claims 187-194, wherein the anti-cancer therapy is bendamustine and rituximab.

200. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib.
201. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib and dexamethasone.
202. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib and rituximab.
203. The method of any one of claims 187-194, wherein the anti-cancer therapy is bortezomib, rituximab, and dexamethasone.
204. The method of any one of claims 187-194, wherein the anti-cancer therapy is chlorambucil.
205. The method of any one of claims 187-194, wherein the anti-cancer therapy is cladribine.
206. The method of any one of claims 187-194, wherein the anti-cancer therapy is cladribine and rituximab.
207. The method of any one of claims 187-194, wherein the anti-cancer therapy is cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (i.e., CHOP-R).
208. The method of any one of claims 187-194, wherein the anti-cancer therapy is cyclophosphamide, prednisone, and rituximab (i.e., CPR).
209. The method of any one of claims 187-194, wherein the anti-cancer therapy is fludarabine.
210. The method of any one of claims 187-194, wherein the anti-cancer therapy is fludarabine and rituximab.
211. The method of any one of claims 187-194, wherein the anti-cancer therapy is fludarabine, cyclophosphamide, and rituximab.

212. The method of any one of claims 187-194, wherein the anti-cancer therapy is rituximab.
213. The method of any one of claims 187-194, wherein the anti-cancer therapy is rituximab, cyclophosphamide, and dexamethasone (i.e., RCD).
214. The method of any one of claims 187-194, wherein the anti-cancer therapy is thalidomide.
215. The method of any one of claims 187-194, wherein the anti-cancer therapy is thalidomide and rituximab.
216. The method of any one of claims 187-194, wherein the anti-cancer therapy is venetoclax.
217. The method of any one of claims 187-194, wherein the anti-cancer therapy is cyclophosphamide, bortezomib, and dexamethasone (i.e., R-CyBorD).
218. The method of any one of claims 187-194, wherein the anti-cancer therapy a hypomethylating agent.
219. The method of any one of claims 1-218, wherein the subject has previously received at least 6 cycles of a hypomethylating agent.
220. The method of any one of claims 1-219, wherein the subject has previously received etoposide chemo-mobilization therapy.
221. The method of any one of claims 1-220, wherein the subject has previously received a bone marrow transplant.
222. The method of any one of claims 1-221, wherein the subject has previously received a hematopoietic cell transplantation.
223. The method of any one of claims 1-222, wherein the subject has previously received a stem cell transplant.

224. The method of any one of claims 1-223, wherein the subject has previously received an autologous stem cell transplant.
225. The method of any one of claims 1-224, wherein the subject has previously received an allogenic stem cell transplant.
226. The method of any one of claims 1-225, wherein the subject has previously received carmustine, etoposide, cytarabine, and melphalan (i.e., BEAM conditioning).
227. The method of any one of claims 1-226, wherein the subject has previously received re-induction therapy.
228. The method of any one of claims 187-227, wherein the subject has previously achieved a partial response.
229. The method of any one of claims 187-227, wherein the subject has previously achieved a good partial response.
230. The method of any one of claims 187-227, wherein the subject has previously achieved a complete response.
231. The method of any one of claims 1-230, wherein the subject has a mutation in RICTOR.
232. The method of any one of claims 1-231, wherein the subject has a N1065S mutation in RICTOR.
233. The method of any one of claims 1-232, wherein the subject has a mutation in MYD88.
234. The method of any one of claims 1-233, wherein the subject has a L265P mutation in MYD88.
235. The method of any one of claims 1-234, wherein the subject has a mutation in TET2.

236. The method of any one of claims 1-235, wherein the subject does not have a mutation in CXCR4.

237. The method of any one of claims 1-235, wherein the subject has a mutation in CXCR4.

238. The method of any one of claims 1-237, wherein the subject shows early progression.

239. The method of any one of claims 1-238, wherein the subject has not previously received a BTK inhibitor.

240. The method of any one of claims 1-239, wherein following administration of the IRAK4 inhibitor, the subject achieves a partial response.

241. The method of any one of claims 1-239, wherein following administration of the IRAK4 inhibitor, the subject achieves a good partial response.

242. The method of any one of claims 1-239, wherein following administration of the IRAK4 inhibitor, the subject achieves a complete response.

243. The method of any one of claims 1-242, wherein following administration of the IRAK4 inhibitor, the subjects IL-1 induced signaling decreases.

244. The method of any one of claims 1-243, wherein following administration of the IRAK4 inhibitor, the subject's cytokine production decreases.

245. The method of any one of claims 1-244, wherein the IRAK4 inhibitor is administered until disease progression or unacceptable toxicity.

246. A method for detecting elevated expression of NF- κ B p-p50 in a biological sample comprising:

contacting the biological sample with a first antibody specific for NF- κ B p-p50, thereby providing an antibody-NF- κ B p-p50 conjugate;

contacting the antibody-NF- κ B p-p50 conjugate with a second antibody thereby providing an antibody/antibody conjugate mixture, wherein the second antibody is specific for the first antibody and the second antibody has enzymatic activity;
treating the antibody/antibody conjugate mixture with a chromogenic substrate for the enzymatic activity, thereby providing a substrate/antibody/antibody conjugate mixture; and
counterstaining the substrate/antibody/antibody conjugate mixture.

247. The method of claim 246, wherein counterstaining the substrate/antibody/antibody conjugate mixture is performed for no more than 60 seconds.

248. The method of claim 246, wherein counterstaining the substrate/antibody/antibody conjugate mixture is performed for no more than 10 seconds.

249. The method of any one of claims 246-248, wherein the counterstain is hematoxylin.

250. The method of any one of claims 246-249, wherein the enzymatic activity is peroxidase activity.

251. The method of claim 250, wherein the chromogenic substrate is a peroxidase substrate.

252. The method of any one of claims 246-249, wherein the enzymatic activity is alkaline phosphatase activity.

253. The method of claim 252, wherein the chromogenic substrate is a phosphatase substrate.

254. The method of any one of claims 246-253, wherein the first antibody is a monoclonal antibody.

255. The method of any one of claims 246-254, wherein the second antibody is a monoclonal antibody.