TREATMENT OF CANCER WITH AN AKT1 INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Patent Application No. 63/570,700, filed on March 27, 2024; and U.S. Patent Application No. 63/574,159, filed on April 3, 2024, all of which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] AKT is a protein kinase that mediates cell survival and proliferation by inhibiting pathways which promote apoptosis. AKT signaling cascade dysfunction is observed in several cancer types and may be associated with tumor aggressiveness. Additionally, aberrant activation of AKT typically leads to enhanced proliferation, growth, survival, and resistance to apoptosis. Pharmaceutical agents with the ability to modulate AKT1 activity would be useful in the treatment of disease, such as cancer.

BRIEF SUMMARY OF THE INVENTION

[0003] One embodiment provides a method of treating a cancer in a patient in need thereof, the method comprising administering to the patient 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

[0004] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

[0005] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient:

(a) a composition comprising 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof; and

(b) at least one oncology therapeutic selected from an endocrine therapy, a hormonal therapy, an aromatase inhibitor, a selective estrogen receptor modulator (SERM) therapy, a selective estrogen receptor degrader (SERD) therapy, an anti-androgen, an androgen deprivation therapy, a taxane, a platinum agent, an anthracycline, an anti-metabolite, an alkylating agent, a microtubule affecting agent, an immune checkpoint inhibitor, a kinase inhibitor, a phosphatidylinositol 3-kinase (PI3K) inhibitor, a human epidermal growth factor

receptor 2 (HER2) inhibitor, an antibody, a poly-ADP ribose polymerase (PARP) inhibitor, an antibody drug conjugate (ADC), a radiopharmaceutical, a neurotrophic tyrosine receptor kinase (NTRK) inhibitor, a rearranged during transfection (RET) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a mammalian target of rapamycin (mTOR) inhibitor, a rapidly accelerated fibrosarcoma (RAF) inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, or a cyclin dependent kinase (CDK) inhibitor.

[0006] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient:

(a) a composition comprising 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof; and

(b) at least one oncology therapeutic selected from CAR-T therapy, tumor-infiltrating lymphocytes (TIL) or a neoantigen vaccine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0008] **Figure 1A**, **Figure 1B**, and **Figure 1C** provide the results from human breast cancer (HR+ HER2-low) patient derived xenograft tumor studies.

[0009] **Figure 2A**, **Figure 2B**, and **Figure 2C** provide the results from endometrial cancer patient derived xenograft tumor studies.

[0010] **Figure 3A**, **Figure 3B**, and **Figure 3C** provide the results from triple negative breast cancer (TNBC) patient derived xenograft tumor studies.

[0011] **Figure 4A**, **Figure 4B**, and **Figure 4C** provide the results from human breast cancer (HR+ HER2-low) patient derived xenograft tumor studies.

INCORPORATION BY REFERENCE

[0012] All publications, patents, and patent applications mentioned in this specification are hereby incorporated by reference for the specific purposes identified herein.

DETAILED DESCRIPTION

Certain Terminology

[0013] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub-combinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0014] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0015] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of the heterocyclic AKT1 inhibitor described herein is intended to encompass all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0016] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids (such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc.) and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic

acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997)). Acid addition salts of basic compounds are, in some embodiments, prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0017] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts are, in some embodiments, formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. See Berge et al., supra.

[0018] "Pharmaceutically acceptable solvate" refers to a composition of matter that is the solvent addition form. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of making with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the

processes described herein. The compounds provided herein optionally exist in unsolvated as well as solvated forms.

[0019] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0020] As used herein, “treatment” or “treating,” or “palliating” or “ameliorating” are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to a therapeutic benefit. The term “therapeutic benefit” is meant include eradication or amelioration of the underlying disorder being treated. Also, a “therapeutic benefit” is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the underlying disorder. For prophylactic benefit, the compositions are, in some embodiments, administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made. The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. In some embodiments, the term “treating” includes slowing or delaying the progression of the disease or disorder to which the term is applied. Additionally, in some embodiments, the term “treating” is applied to one or more of the complications resulting from the disease or disorder to which the term is applied. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above. In some embodiments, the treatment provides a partial response. A partial response, or partial remission, is a decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment. In some embodiments, the treatment provides a complete response. A complete response, or complete remission, is the disappearance of all signs of cancer in response to treatment. In some embodiments, the treatment provides a slowing of disease progression.

[0021] The term "tumor," or “cancer” as used herein, and unless otherwise specified, refers to a neoplastic cell growth, and includes pre-cancerous and cancerous cells and tissues. Tumors usually present as a lesion or lump. As used herein, “treating” a tumor means that has one or

more symptoms of the disease, such as the tumor itself, vascularization of the tumor, or other parameters by which the disease is characterized, are reduced, ameliorated, inhibited, placed in a state of remission, or maintained in a state of remission. “Treating” a tumor also means that one or more hallmarks of the tumor may be eliminated, reduced, or prevented by the treatment. Non-limiting examples of such hallmarks include uncontrolled degradation of the basement membrane and proximal extracellular matrix, migration, division, and organization of the endothelial cells into new functioning capillaries, and the persistence of such functioning capillaries.

[0022] The term “refractory” or “refractory to therapy” indicates that the patients have never responded to therapy.

[0023] The term “relapsed” or “relapsed after therapy” indicates that patients, after initially responding to prior therapy, have progressive disease due to acquired resistance and/or intolerance.

[0024] The term “resistance to therapy” or “acquired resistance to therapy” indicates the patients, after initially responding to prior therapy, have progressive disease due to clinical or molecular resistance to the therapy. The acquired resistance can result from emergence of resistant mutations in the molecular target of the therapy, or in the development of physiological functions such as efflux pumps.

[0025] The phrase "therapeutically effective amount", as used herein, refers to that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

[0026] Other aspects, advantages, and features of the invention will become apparent from the detailed description below.

AKT1 Activation and Intracellular Signaling Pathways

[0027] The serine/threonine kinase AKT (also known as protein kinase B (PKB)) is a key component of the phosphoinositide-3-kinase (PI3K)/AKT signaling pathway, as it exerts a pivotal role in cell growth, proliferation, survival, and metabolism. Over the last few decades, the PI3K/AKT signaling pathway has been investigated intensively as dysregulated proteins within this signaling cascade behave as oncogenic drivers in various cancer types. Genomic alterations, such as deletions or mutations in tumor suppressor PTEN, PI3K, and/or AKT can result in enhanced pathway activity. These genetic alterations can lead to the hyperactivation of AKT, abnormally activating a major signaling node within the PI3K/AKT pathway.

[0028] AKT proteins play a crucial role within the PI3K/AKT pathway, modulating major cellular functions including cell cycle progression, cell size, regulation of glucose metabolism, transcription, protein synthesis, genome stability, and neovascularization. For example, AKT directly phosphorylates the tumor suppressor tuberous sclerosis 2 (TSC2) at S939/T1462 and impairs its stability, leading to the release of its inhibitory effect on mTOR. In turn, activated mTOR transduces the growth factors signaling to downstream targets such as p70 ribosomal S6 kinase (S6K1) and eukaryotic translation initiation factor 4E binding protein 1, leading to increased protein translation. mTOR is a key component in the AKT signaling pathway, which is a downstream member of AKT and an important regulator for cell metabolism and growth. mTOR is also an activator which can directly phosphorylate AKT's regulatory serine residue, Ser473. mTOR forms a complex with rapamycin-insensitive companion of mTOR (RICTOR) (and other proteins) to form mTOR complex 2 (mTORC2), which can directly phosphorylate AKT Ser473. AKT can affect cell survival and growth because it can influence the tuberous sclerosis complex (TSC) 1/2 along the mTORC signaling pathway and inhibit pro-apoptotic proteins or signals. In addition, AKT is able to phosphorylate and activate cAMP responsive element binding protein 1, which also plays important roles in tumorigenesis.

[0029] AKT proteins also play a role blocking apoptosis through the inactivation of pro-apoptotic proteins, and mediate cellular growth factors, promoting cell survival. AKT is also a major downstream effector of nuclear factor-kappaB (NfκB), which may link AKT signaling to the nucleus of a cell. Furthermore, AKT is a key downstream mediator of the phosphoinositide-3-kinase (PI3K) signaling pathway. Adding to the complexity of the PI3K/AKT signaling pathway, PI3Ks can be activated by several different pathways. For example, Class I PI3Ks, PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, are activated by a cascade of activated receptor tyrosine kinase (RTK) and recruitment of growth factor receptor-bound protein 2 (GRB2), whereby GRB2 recruits the RAS family of GTPases to directly interact with and activate Class I PI3Ks. Alternatively, PI3K activation can proceed directly from interactions with RTKs or G-protein-coupled receptors (GPCRs). Consequently, the AKT cascade is activated by either RTKs or GPCRs, along with other signals including integrins, B cell receptors, T cell receptors, and cytokine receptors. Given the complexity of the AKT signaling cascade, it is unsurprising that multiple studies have shown that hyperactivation in this pathway frequently results in various cancers, such as, but not limited to, breast cancer, endometrial cancer, uterine cancer, cervical cancer, gastric carcinoma, glioblastoma, gliosarcomas, head and neck squamous cell carcinoma, ovarian cancer, pancreatic cancer,

and prostate cancer, and are often associated with tumor aggressiveness (Nitulescu, G. M. et al., Int J Oncol., 2018; 53(6): 2319-2331).

AKT1 Kinase

[0030] AKT is a key downstream mediator of the highly complex PI3K signaling pathway, as AKT can directly phosphorylate many proteins that are involved in diverse cellular processes, including cell proliferation, survival, migration, and metabolism.

[0031] The complexity of this pathway is compounded by the presence of three AKT isoforms in mammals, AKT1, AKT2, and AKT3. While the isoforms are encoded by different genes, they are highly homologous at the protein level and share a conserved domain structure comprising an N-terminal pleckstrin homology (PH) domain, a kinase domain, and a C-terminal regulatory domain comprising a hydrophobic moiety, which includes the regulatory serine residue (Nitulescu, G. M. et al., Int J Oncol., 2018; 53(6): 2319-2331). Though the AKT isoforms share a high sequence homology, they differ in their intracellular, cellular, and tissue functions and localizations, resulting in a highly complex signaling pathway with over a hundred downstream substrates. Each of the 3 mammalian AKT isoforms have overlapping as well as distinct functions. For example, AKT1 is ubiquitously expressed, whereas AKT2 is primarily expressed in insulin-responsive tissues, and AKT3 is primarily expressed in the brain and testes.

[0032] AKT is known as a survival kinase and mediates cell survival and proliferation by regulatory inhibition of apoptotic pathways through phosphorylation of BAD or MDM2 and regulation of Bcl2 expression. Malfunctions of AKT manifested as aberrantly increased activity typically lead to enhanced proliferation, growth, survival, and resistance to apoptosis (Alwhaibi, A. et al., Pharmacol Res., 2019, 145: 104270). For example, enhanced activation of all three AKT isoforms has been implicated in tumor development and progression, as shown in gastric, glioma, melanoma, breast, endometrial, uterine, ovarian, pancreatic, colorectal, and prostate cancers among others. Additionally, AKT1 has been found to be involved in invasion and migration of cancerous cells (Alwhaibi, A. et al., Pharmacol Res., 2019, 145: 104270). Researchers found that silencing the AKT1 isoform can abrogate specific types of cancer cell migration. However, there have been other studies which have demonstrated that activated AKT1 resulted in less metastatic propensity for lung metastatic lesion cells and breast cancer cells. AKT1 has also been identified as a key protein involved in angiogenesis, lung cancer, and tumorigenesis. These features make AKT a highly attractive target for treatment options.

[0033] Many kinase inhibitors (including AKT inhibitors) target a catalytic domain within the protein. However, the three AKT isoforms share a phosphorylation site in the catalytic domain corresponding to a threonine residue; specifically, Thr308 in AKT1, Thr309 in AKT2, and Thr305 in AKT3. The three AKT isoforms are activated by a second phosphorylation in the C-terminus of the protein at a regulatory serine residue; specifically, Ser473 in AKT1, Ser474 in AKT2, and Ser472 in AKT3. Known phosphorylating agents of AKT1 at Ser473 include, but are not limited to PDK-1, integrin-linked kinase (ILK), members of the PI3K-related kinase (PIKK) family, and mammalian target of rapamycin (mTOR) (Nitulescu, G. M. et al., Int J Oncol., 2018; 53(6): 2319-2331). The high sequence homology of the AKT isoforms has proved challenging in regard to the selectivity of AKT inhibitors, resulting in dose-limiting side effects during treatment and a lack of efficacy. Thus, there remains a need to identify AKT mutant-specific and AKT isoform-selective treatment options.

[0034] The most common mutation among AKT isoforms reported across all cancers is the somatic AKT1-E17K mutation. It has been determined that the AKT1 gene mutation E17K can affect cell growth, proliferation, survival, and migration of breast cancer cells, colorectal cancer cells, and ovarian cancer cells (Chen, Y. et al., Front Cell Dev Biol., 2020; 8: 573599). These mutations in the PH structural domain increase the binding of AKT1 to Phosphatidylinositol-3,4,5-triphosphate (PIP3) lipid ligand, which accelerates transfer of AKT from the cytoplasm to the cell membrane through direct interactions between the PH domain of AKT and the phosphatidylinositol headgroup. Transfer of AKT onto the cell membrane allows it to be further phosphorylated and activated. Once fully activated, AKT can return to the cytoplasm, or go to the nucleus, or other intracellular sites, and phosphorylate other substrate proteins to regulate cell function.

[0035] Somatic cell mutations can be a major driver in activating the PI3K-AKT signaling pathway, with the E17K mutation being the highest frequency of AKT1 mutations. This mutation is nearly exclusively present in AKT1. The AKT1 E17K mutation has been shown to mediate the PI3K-AKT signaling cascade by expanding PIP lipid specificity, which causes conformational changes. This also enhances subcellular localization to accelerate localization of the PH structural domain to the plasma membrane. Additionally, the E17K mutation increases PIP3 binding specificity by 7-fold and phosphatidylinositol-(4,5)-bisphosphate (PIP2) by 100-fold. The AKT1 E17K mutation also causes rapid conformational changes in the AKT1 PH structural domain. The conformational changes to this domain result in a 4.5-fold increase in its membrane localization, which can result in excessive phosphorylation and

activation. The AKT1 E17K mutation can also result in enhanced subcellular localization by increasing the transient expression.

[0036] The AKT1 E17K mutation is a recurrent somatic cell mutation predominantly in breast cancer, uterine cancer, endometrial cancers, ovarian cancer, prostate cancer, meningioma, and in the somatic mosaic overgrowth disease Proteus syndrome. Activating mutations and overexpression of AKT has been correlated to resistance to chemotherapeutic agents such as cisplatin, methotrexate, and paclitaxel. For example, the E17K mutation enhances migration of breast cancer cells, and also enhances resistance to chemotherapeutic drugs. Given the conformational and signaling effects of the AKT1 E17K mutation, and its prevalence in various cancers, the AKT1 E17K mutation poses a useful target for the targeted treatment of cancers.

Prior Art AKT1 Inhibitors

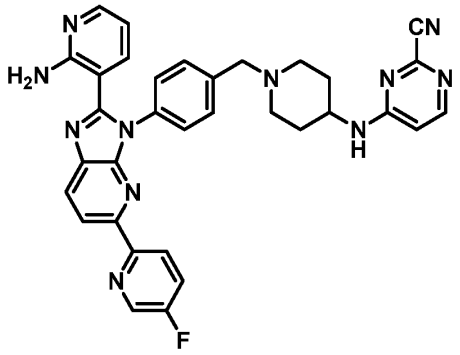
[0037] Most AKT inhibitors targeting the ATP binding site are non-selective against the three isoforms, as well as having little to no selectivity for the hyperactivated mutant forms of AKT or against other structurally similar kinases. These ATP targeting inhibitors are classified as aminofurazans, azepane derivatives, isoquinoline-5-sulfonamides, phenylpyrazole derivatives, thiophene carboxamide derivatives, and thiazole carboxamide derivatives. Additionally, there are ATP non-competitive AKT inhibitors which are allosteric modulators which have greater specificity for AKT versus other kinases than the ATP targeting inhibitors. Many of these allosteric modulator inhibitors are classified as purine derivatives, thiourea derivatives, alkylphospholipids, sulfonamides, 2,3-diphenylquinoxaline analogs, and indole-3-carbinol derivatives. Prior art AKT inhibitors include, but are not limited to, ipatasertib, capivasertib, PF-04691502, AT7867, GSK690693, CCT12893, AZD536, MK-2206, miransertib, uprosertib, and afureserti.

[0038] In cancer treatment, AKT inhibitor monotherapy often relies on PI3K/AKT pathway alterations upstream of AKT, and treatments are often associated with adverse side-effects. Furthermore, despite the multitude of AKT inhibitors that have entered clinical studies for the treatment of cancer, very few have reached phase III in clinical trials, highlighting the complexity of the AKT-signaling pathway and associated malfunctions and the toxicity associated with inhibiting wildtype (non-mutant) forms of AKT. For example, one of the major on-target side effects of PI3K and AKT inhibitors is hyperglycemia, where patients may require treatment with anti-hyperglycemic medication, such as insulin and/or metformin. Consequently, patients with Type I diabetes, insulin-dependent diabetes, diabetes requiring metformin, or pre-diabetes treated with metformin are ineligible for treatment with the

currently available AKT inhibitors. Thus, there remains a need to develop new and novel AKT inhibitors, which can offer greater specificity for the mutant AKT form or a specific AKT isoform, reduced side-effects, and lower toxicity compared to the aforementioned compounds.

Novel Heterocyclic AKT1 Inhibitor

[0039] One of the heterocyclic AKT1 inhibitors described herein is Compound 1, having the structure below, and the chemical name 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile. The synthesis and characterization of Compound 1 was presented in WO 2024/073371.



Compound 1

Cancer and Methods of Treatment

[0040] One embodiment provides a method of treating a cancer in a patient in need thereof, the method comprising administering to the patient 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

[0041] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

[0042] Another embodiment provides the method, wherein the oral administration occurs every other day, once per day, twice per day, or three times per day.

[0043] Oral doses typically range from about 1.0 mg to about 1500 mg, one to four times, or more, per day.

[0044] One embodiment provides a compound provided herein, or pharmaceutically acceptable salt or solvate thereof, for use in a method of treating cancer in a patient in need thereof. Another embodiment provides use of a compound provided herein, or pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of cancer.

[0045] One embodiment provides the method wherein the cancer is breast cancer. Another embodiment provides the method wherein the cancer is a hormone receptor positive (HR+) breast cancer. Another embodiment provides the method wherein the cancer is a human epidermal growth factor receptor 2 negative (HER2-) breast cancer. Another embodiment provides the method wherein the cancer is a HR+/HER2- breast cancer. Another embodiment provides the method wherein the cancer is a HR+/HER2-low breast cancer. Another embodiment provides the method wherein the cancer is a HR+/HER2+ breast cancer.

[0046] Another embodiment provides the method wherein the cancer is a triple negative breast cancer (TNBC). Another embodiment provides the method wherein the cancer is an invasive breast cancer. Another embodiment provides the method wherein the patient has shown progression on at least one CDK4/6 inhibitor. Another embodiment provides the method wherein the patient has shown progression on at least one endocrine-based regimen.

[0047] One embodiment provides the method wherein the cancer is uterine cancer. Another embodiment provides the method wherein the cancer is uterine sarcoma. Another embodiment provides the method wherein the cancer is endometrial cancer. Another embodiment provides the method wherein the cancer is Type I endometrial cancer.

[0048] One embodiment provides the method wherein the cancer is Type II endometrial cancer.

[0049] Another embodiment provides the method wherein the cancer is Type II endometrial papillary serous carcinoma. Another embodiment provides the method wherein the cancer is Type II endometrial clear cell carcinoma. Another embodiment provides the method wherein the cancer is Type II endometrial undifferentiated carcinoma. Another embodiment provides the method wherein the cancer is Type II endometrioid carcinoma. Another embodiment provides the method wherein the cancer is microsatellite instability (MSI) high and/or DNA mismatch repair (MMR) deficient. Another embodiment provides the method wherein the cancer is tumor mutational burden (TMB) high. Another embodiment provides the method wherein the cancer is HER2-.

[0050] One embodiment provides the method wherein the cancer is cervical cancer. Another embodiment provides the method wherein the cancer is a cervical squamous cell carcinoma.

[0051] Another embodiment provides the method wherein the cancer is a cervical adenocarcinoma.

[0052] One embodiment provides the method wherein the cancer is prostate cancer. Another embodiment provides the method wherein the cancer is prostate adenocarcinoma.

[0053] Another embodiment provides the method wherein the cancer is prostate neuroendocrine cancer. Another embodiment provides the method wherein the cancer is prostate small cell neuroendocrine cancer. Another embodiment provides the method wherein the cancer is prostate large cell carcinoma. Another embodiment provides the method wherein the cancer is prostate transitional cell carcinoma. Another embodiment provides the method wherein the cancer is prostate sarcoma.

[0054] One embodiment provides the method wherein the cancer is bladder cancer. Another embodiment provides the method wherein the cancer is urothelial cancer. Another embodiment provides the method wherein the cancer is squamous cell cancer of the bladder. Another embodiment provides the method wherein the cancer is small cell cancer of the bladder. Another embodiment provides the method wherein the cancer is adenocarcinoma of the bladder.

[0055] One embodiment provides the method wherein the cancer is lung cancer.

[0056] One embodiment provides the method wherein the cancer is non-small cell lung cancer.

[0057] One embodiment provides the method wherein the cancer is non-squamous non-small cell lung cancer.

[0058] One embodiment provides the method wherein the cancer is squamous non-small cell lung cancer.

[0059] One embodiment provides the method wherein the cancer is colon cancer.

[0060] One embodiment provides the method wherein the cancer is anal cancer.

[0061] One embodiment provides the method wherein the cancer is a meningioma.

[0062] One embodiment provides the method wherein the cancer is a glioma.

[0063] One embodiment provides the method wherein the cancer is pancreatic cancer. Another embodiment provides the method wherein the cancer is exocrine pancreatic cancer. Another embodiment provides the method wherein the cancer is neuroendocrine pancreatic cancer.

[0064] One embodiment provides the method wherein the cancer is thyroid cancer.

[0065] One embodiment provides the method wherein the cancer is sarcoma. Another embodiment provides the method wherein the cancer is soft tissue sarcoma. Another

embodiment provides the method wherein the cancer is liposarcoma. Another embodiment provides the method wherein the cancer is angiosarcoma. Another embodiment provides the method wherein the cancer is osteosarcoma. Another embodiment provides the method wherein the cancer is leiomyosarcoma. Another embodiment provides the method wherein the cancer is rhabdomyosarcoma. Another embodiment provides the method wherein the cancer is myxofibrosarcoma.

[0066] One embodiment provides the method wherein the cancer is parotid gland cancer.

[0067] One embodiment provides the method wherein the cancer is esophageal cancer.

[0068] One embodiment provides the method wherein the cancer is stomach cancer.

[0069] One embodiment provides the method wherein the cancer is skin cancer. Another embodiment provides the method wherein the cancer is nonmelanoma skin cancer. Another embodiment provides the method wherein the cancer is squamous nonmelanoma skin cancer. Another embodiment provides the method wherein the cancer is non-squamous nonmelanoma skin cancer.

[0070] One embodiment provides the method wherein the cancer is ovarian cancer. Another embodiment provides the method wherein the cancer is epithelial ovarian cancer. Another embodiment provides the method wherein the cancer is serous epithelial ovarian cancer. Another embodiment provides the method wherein the cancer is endometrioid ovarian cancer. Another embodiment provides the method wherein the cancer is clear cell ovarian cancer. Another embodiment provides the method wherein the cancer is mucinous ovarian cancer.

[0071] One embodiment provides the method wherein the cancer is adenoid cystic carcinoma.

[0072] One embodiment provides the method wherein the cancer is renal cell cancer.

[0073] One embodiment provides the method wherein the cancer is appendix cancer.

[0074] One embodiment provides the method wherein the cancer is multiple myeloma.

[0075] One embodiment provides the method wherein the cancer is acute myeloid leukemia.

[0076] One embodiment provides the method wherein the cancer is cancer of unknown primary.

[0077] One embodiment provides the method wherein the cancer is locally advanced.

[0078] One embodiment provides the method wherein the cancer is metastatic.

[0079] One embodiment provides the method wherein the method is adjuvant therapy following surgical resection.

[0080] One embodiment provides the method wherein the method is neo-adjuvant therapy.

[0081] One embodiment provides the method wherein the method is first-line systemic therapy for locally advanced or metastatic disease.

[0082] One embodiment provides the method wherein the patient has relapsed after prior therapy.

[0083] One embodiment provides the method wherein the patient has acquired resistance to prior therapy.

[0084] One embodiment provides the method wherein the patient is refractory to therapy.

[0085] One embodiment provides the method wherein the patient has shown progression on cytotoxic chemotherapy.

[0086] One embodiment provides the method wherein the cancer is characterized by existence of AKT1-E17K mutation.

[0087] One embodiment provides the method wherein the cancer exhibits one or more co-occurring alterations selected from a PIK3CA alteration, a PIK3R1 alteration, an AKT1 alteration, and PTEN alteration.

[0088] One embodiment provides the method wherein the patient exhibits risk factors for hyperglycemia.

[0089] One embodiment provides the method wherein the patient exhibits risk factors selected from obesity, body mass index greater than or equal to 30, fasting blood glucose over 160 mg/dL, HbA1c greater than 6.0.

[0090] One embodiment provides the method wherein the patient exhibits Type I diabetes, diabetes requiring insulin, diabetes requiring metformin or another oral hypoglycemic agent, or pre-diabetes treated with metformin or another oral hypoglycemic agent.

Combination Therapy

[0091] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient:

(a) a composition comprising 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof; and

(b) at least one oncology therapeutic selected from CAR-T therapy, tumor-infiltrating lymphocytes (TIL) or a neoantigen vaccine.

[0092] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient:

(a) a composition comprising 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof; and

(b) at least one oncology therapeutic selected from an endocrine therapy, a hormonal therapy, an aromatase inhibitor, a selective estrogen receptor modulator (SERM) therapy, a selective estrogen receptor degrader (SERD) therapy, an anti-androgen, an androgen deprivation therapy, a taxane, a platinum agent, an anthracycline, an anti-metabolite, an alkylating agent, a microtubule affecting agent, an immune checkpoint inhibitor, a kinase inhibitor, a phosphatidylinositol 3-kinase (PI3K) inhibitor, a human epidermal growth factor receptor 2 (HER2) inhibitor, an antibody, a poly-ADP ribose polymerase (PARP) inhibitor, an antibody drug conjugate (ADC), a radiopharmaceutical, a neurotrophic tyrosine receptor kinase (NTRK) inhibitor, a rearranged during transfection (RET) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a mammalian target of rapamycin (mTOR) inhibitor, a rapidly accelerated fibrosarcoma (RAF) inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, or a cyclin dependent kinase (CDK) inhibitor.

[0093] One embodiment provides the method wherein at least one oncology therapeutic is selected from an endocrine therapy, a hormonal therapy, a SERM therapy, a SERD therapy, an aromatase inhibitor, or an androgen deprivation therapy. Another embodiment provides the method wherein the endocrine therapy, a hormonal therapy, a SERM therapy, a SERD therapy, an aromatase inhibitor, or an androgen deprivation therapy is selected from megestrol, exemestane, anastrozole, letrozole, tamoxifen, torimifene, raloxifene, fulvestrant, camizestrant, elacestrant, amcenestrant, giredestrant, imlunestrant, rintodestrant, SHR9549, ZN-c5, D0502, vepdegrestrant, palazestrant, AC682, DT2216, apalutamide, bicalutamide, darolutamide, enzalutamide, flutamide, nilutamide, abiraterone, buserelin, goserelin, leuprorelin, triptorelin, degarelix, or relugolix,.

[0094] One embodiment provides the method wherein at least one oncology therapeutic is a taxane. Another embodiment provides the method wherein the taxane is selected from paclitaxel, docetaxel, cabazitaxel, or abraxane.

[0095] One embodiment provides the method wherein at least one oncology therapeutic is a platinum agent. Another embodiment provides the method wherein the platinum agent is selected from cisplatin, carboplatin, or oxaliplatin.

[0096] One embodiment provides the method wherein at least one oncology therapeutic is an anthracycline. Another embodiment provides the method wherein the anthracycline is selected from doxorubicin or epirubicin.

[0097] One embodiment provides the method wherein at least one oncology therapeutic is an anti-metabolite. Another embodiment provides the method wherein the anti-metabolite is selected from methotrexate, fluorouracil, pemetrexed, irinotecan, topotecan, capecitabine or gemcitabine.

[0098] One embodiment provides the method wherein at least one oncology therapeutic is an alkylating agent. Another embodiment provides the method wherein the alkylating agent is selected from ifosfamide, trabectedin, cyclophosphamide, melphalan, or dacarbazine.

[0099] One embodiment provides the method wherein at least one oncology therapeutic is a microtubule affecting agent. Another embodiment provides the method wherein the microtubule affecting agent is selected from ixabepilone, viborelbine, or eribulin.

[00100] One embodiment provides the method wherein at least one oncology therapeutic is an immune checkpoint inhibitor. Another embodiment provides the method wherein the immune checkpoint inhibitor is selected from a CTLA-4 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, or a bi-specific PD-1/CTLA4 inhibitor.

[00101] One embodiment provides the method wherein the CTLA-4 inhibitor is selected from ipilimumab or tremelimumab. Another embodiment provides the method wherein the PD-1 inhibitor is selected from spartalizumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab, dostarlimab, retifanlimab, or toripalimab. Another embodiment provides the method wherein the bi-specific PD-1/CTLA4 inhibitor is selected from AK104, MGD019, XmAb20717, or MEDI5752.

[00102] One embodiment provides the method wherein at least one oncology therapeutic is a kinase inhibitor. Another embodiment provides the method wherein the kinase inhibitor is selected from lenvatinib, pazopanib, imatinib, sorafenib, or avutometinib.

[00103] One embodiment provides the method wherein at least one oncology therapeutic is a PI3K inhibitor. Another embodiment provides the method wherein the PI3K inhibitor is selected from copanlisib, alpelisib, idelalisib, duvelisib, umbralisib, or STX-478.

[00104] One embodiment provides the method wherein at least one oncology therapeutic is a HER2 inhibitor. Another embodiment provides the method wherein the HER2 inhibitor is selected from lapatinib, neratinib, tucatinib, pyrotinib, or afatinib.

[00105] One embodiment provides the method wherein at least one oncology therapeutic is an antibody. Another embodiment provides the method wherein the antibody is selected from trastuzumab, pertuzumab, margetuxumab, bevacizumab, or rituximab.

[00106] One embodiment provides the method wherein at least one oncology therapeutic is a PARP inhibitor. Another embodiment provides the method wherein the PARP inhibitor is selected from olaparib, rucaparib, talazoparib, or niraparib.

[00107] One embodiment provides the method wherein at least one oncology therapeutic is an ADC. Another embodiment provides the method wherein the antibody drug conjugate is selected from ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, sacituzumab govitecan, disitamab vedotin, tisotumab vedotin, raludotatug deruxtecan, ARX-788, datopotamab deruxtecan, patritumab deruxtecan, ladiratuzumab vedotin, HS-20089, pertuzumab, or margetuximab.

[00108] One embodiment provides the method wherein at least one oncology therapeutic is a radiopharmaceutical. Another embodiment provides the method wherein the radiopharmaceutical is [111In]/[89Zr]-trastuzumab.

[00109] One embodiment provides the method wherein at least one oncology therapeutic is a NTRK inhibitor. Another embodiment provides the method wherein the NTRK inhibitor is selected from entrectinib or larotrectinib.

[00110] One embodiment provides the method wherein at least one oncology therapeutic is a RET inhibitor. Another embodiment provides the method wherein the RET inhibitor is selpercatinib or pralsetinib.

[00111] One embodiment provides the method wherein at least one oncology therapeutic is an EGFR inhibitor. Another embodiment provides the method wherein the EGFR inhibitor is erlotinib, osimertinib, neratinib, cetuximab, gefitinib, panitumumab, dacomitinib, afatinib, lapatinib, necitumumab, mobocertinib, or vandetanib.

[00112] One embodiment provides the method wherein at least one oncology therapeutic is a mTOR inhibitor. Another embodiment provides the method wherein the mTOR inhibitor is deforolimus, everolimus, sirolimus, or temsirolimus.

[00113] One embodiment provides the method wherein at least one oncology therapeutic is a RAF inhibitor. Another embodiment provides the method wherein the RAF inhibitor is vemurafenib, dabrafenib, encorafenib, tovorafenib, naporafenib, belvarafenib, or exarafenib.

[00114] One embodiment provides the method wherein at least one oncology therapeutic is a MEK inhibitor. Another embodiment provides the method wherein the MEK inhibitor is binimetinib, cobimetinib, trametinib, selumetinib, pimasertib, avutometinib, IMM-1-104, or NST-628.

[00115] One embodiment provides the method wherein at least one oncology therapeutic is a CDK inhibitor. Another embodiment provides the method wherein the CDK inhibitor is

selected from palbociclib, abemaciclib, ribociclib, tagtociclib, ebvaciclib, lerociclib, PF-07220060, BLU-222, INX-315, or AVZO-021.

[00116] One embodiment provides the method wherein the cancer is lung cancer.

[00117] One embodiment provides the method wherein the cancer is non-small cell lung cancer.

[00118] One embodiment provides the method wherein the cancer is non-squamous non-small cell lung cancer.

[00119] One embodiment provides the method wherein the cancer is squamous non-small cell lung cancer.

[00120] One embodiment provides the method wherein the cancer is colon cancer.

[00121] One embodiment provides the method wherein the cancer is anal cancer.

[00122] One embodiment provides the method wherein the cancer is a meningioma.

[00123] One embodiment provides the method wherein the cancer is a glioma.

[00124] One embodiment provides the method wherein the cancer is pancreatic cancer. Another embodiment provides the method wherein the cancer is exocrine pancreatic cancer. Another embodiment provides the method wherein the cancer is neuroendocrine pancreatic cancer.

[00125] One embodiment provides the method wherein the cancer is thyroid cancer.

[00126] One embodiment provides the method wherein the cancer is sarcoma. Another embodiment provides the method wherein the cancer is soft tissue sarcoma. Another embodiment provides the method wherein the cancer is liposarcoma. Another embodiment provides the method wherein the cancer is angiosarcoma. Another embodiment provides the method wherein the cancer is osteosarcoma. Another embodiment provides the method wherein the cancer is leiomyosarcoma. Another embodiment provides the method wherein the cancer is rhabdomyosarcoma. Another embodiment provides the method wherein the cancer is myxofibrosarcoma.

[00127] One embodiment provides the method wherein the cancer is parotid gland cancer.

[00128] One embodiment provides the method wherein the cancer is esophageal cancer.

[00129] One embodiment provides the method wherein the cancer is stomach cancer.

[00130] One embodiment provides the method wherein the cancer is skin cancer. Another embodiment provides the method wherein the cancer is nonmelanoma skin cancer. Another embodiment provides the method wherein the cancer is squamous nonmelanoma

skin cancer. Another embodiment provides the method wherein the cancer is non-squamous nonmelanoma skin cancer.

[00131] One embodiment provides the method wherein the cancer is ovarian cancer. Another embodiment provides the method wherein the cancer is epithelial ovarian cancer. Another embodiment provides the method wherein the cancer is serous epithelial ovarian cancer. Another embodiment provides the method wherein the cancer is endometrioid ovarian cancer. Another embodiment provides the method wherein the cancer is clear cell ovarian cancer. Another embodiment provides the method wherein the cancer is mucinous ovarian cancer.

[00132] One embodiment provides the method wherein the cancer is adenoid cystic carcinoma.

[00133] One embodiment provides the method wherein the cancer is renal cell cancer.

[00134] One embodiment provides the method wherein the cancer is appendix cancer.

[00135] One embodiment provides the method wherein the cancer is multiple myeloma.

[00136] One embodiment provides the method wherein the cancer is acute myeloid leukemia.

[00137] One embodiment provides the method wherein the cancer is cancer of unknown primary.

[00138] One embodiment provides the method wherein the cancer is locally advanced.

[00139] One embodiment provides the method wherein the cancer is metastatic.

[00140] One embodiment provides the method wherein the method is adjuvant therapy following surgical resection.

[00141] One embodiment provides the method wherein the method is neo-adjuvant therapy.

[00142] One embodiment provides the method wherein the method is first-line systemic therapy for locally advanced or metastatic disease.

[00143] One embodiment provides the method wherein the patient has relapsed after prior therapy.

[00144] One embodiment provides the method wherein the patient has acquired resistance to prior therapy.

[00145] One embodiment provides the method wherein the patient is refractory to therapy.

[00146] One embodiment provides the method wherein the patient has shown progression on cytotoxic chemotherapy.

[00147] One embodiment provides the method wherein the cancer is characterized by existence of AKT1-E17K mutation.

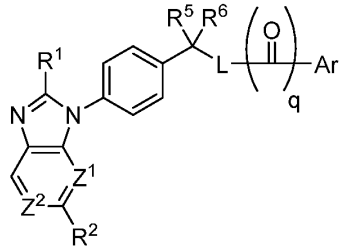
[00148] One embodiment provides the method wherein the cancer exhibits one or more co-occurring alterations selected from a PIK3CA alteration, a PIK3R1 alteration, an AKT1 alteration, and PTEN alteration.

[00149] One embodiment provides the method wherein the patient exhibits risk factors for hyperglycemia.

[00150] One embodiment provides the method wherein the patient exhibits risk factors selected from obesity, body mass index greater than or equal to 30, fasting blood glucose over 160 mg/dL, HbA1c greater than 6.0.

[00151] One embodiment provides the method wherein the patient exhibits Type I diabetes, diabetes requiring insulin, diabetes requiring metformin or another oral hypoglycemic agent, or pre-diabetes treated with metformin or another oral hypoglycemic agent.

[00152] One embodiment provides a method of treating a cancer in a patient in need thereof, the method comprising administering to the patient a compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof:



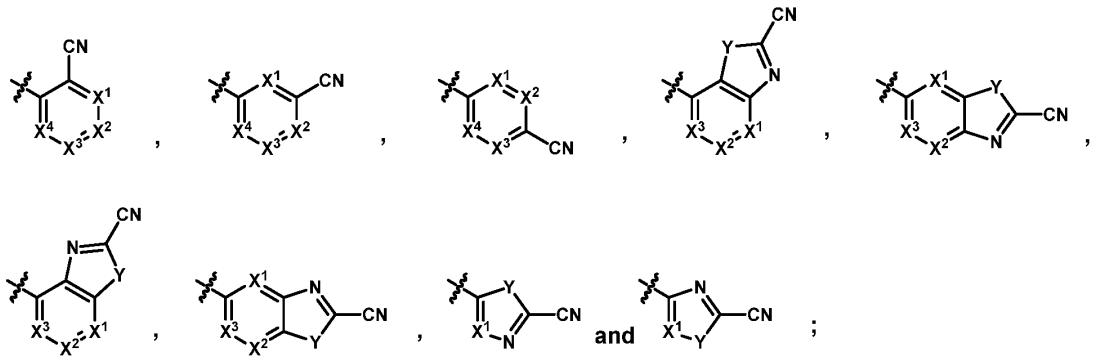
(Ib)

wherein:

Z^1 is N, C-H, or C-R^3;

Z^2 is N, C-H, or C-R^4;

Ar is selected from:



X^1 is N or C-R^7;

X^2 is N or C-R^7:

X^3 is N or C-R^7;

X^4 is N or C-R^7;

Y is O, S, or N-R^9;

R^1 is selected from optionally substituted aryl, or optionally substituted heteroaryl;

R^2 is selected from hydrogen, optionally substituted C1-C6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl;

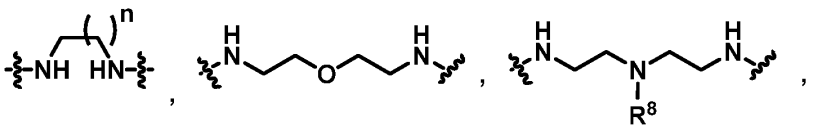
R^3 is selected from optionally substituted C1-C6 alkyl, or optionally substituted aryl;

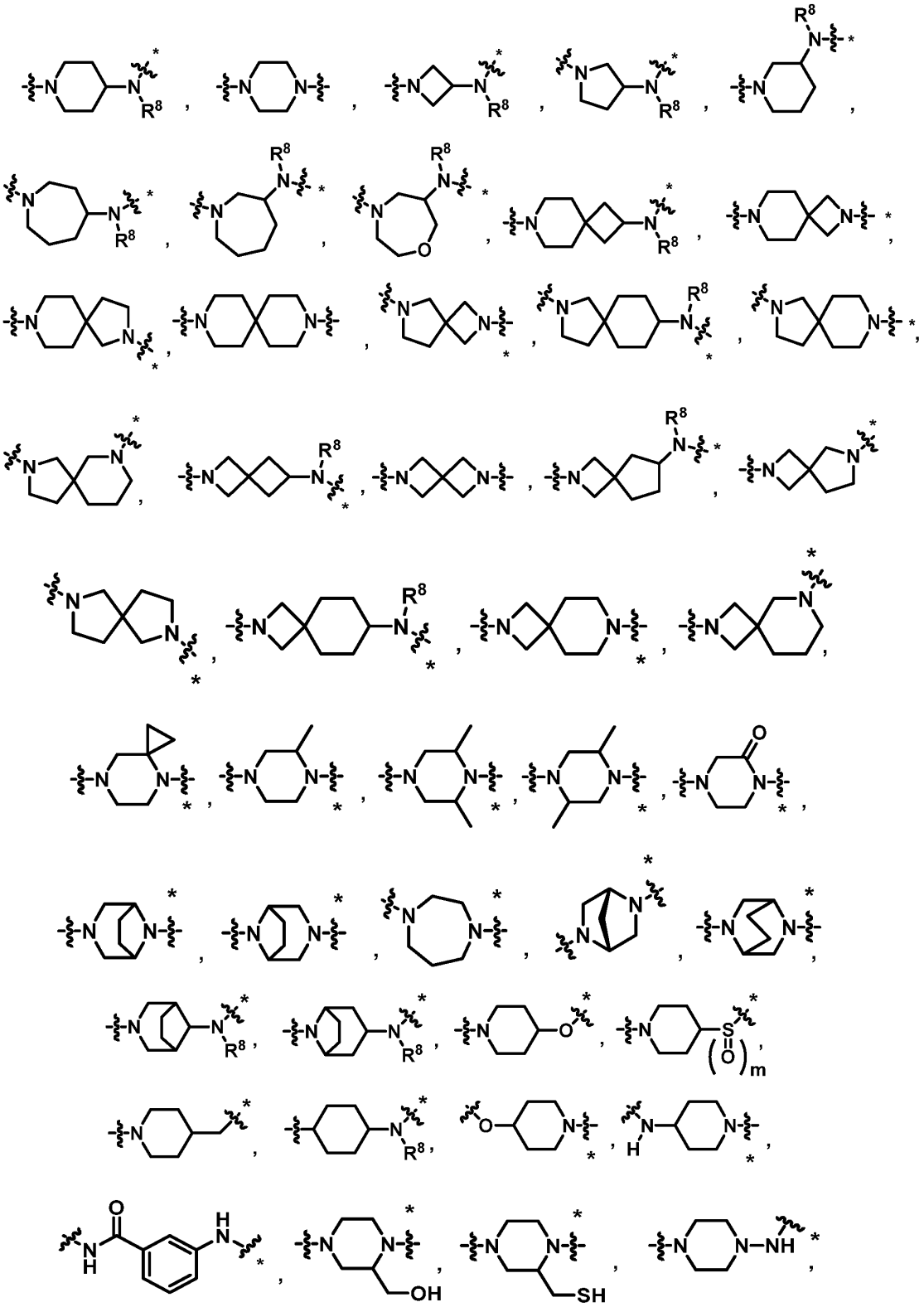
R^4 is selected from optionally substituted C1-C6 alkyl, or optionally substituted aryl;

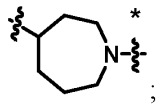
R^5 and R^6 are each independently hydrogen, deuterium, halogen, -OH, or optionally substituted C1-C6 alkyl; or R^5 and R^6 together form an oxo; or R^5 and R^6 join together to form a carbocycle or heterocycle;

each R^7 is independently selected from hydrogen, deuterium, halogen, -OH, -SH, optionally substituted Cl-C6 alkoxy, -S-(optionally substituted C1-C6 alkyl), -CN, optionally substituted Cl-C6 alkyl, and optionally substituted aryl;

L is a divalent radical selected from:





and ;

wherein the asterisk (*) indicates the bond to the –(C(O))q-Ar group;

R^8 is hydrogen, optionally substituted C1-C6 alkyl, optionally substituted C3-C7 cycloalkyl, or optionally substituted heterocyclyl;

R^9 is hydrogen, or optionally substituted C1-C6 alkyl;

m is 0, 1, or 2;

n is 1, 2, or 3; and

q is 0 or 1.

[00153] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has Z^1 is N.

[00154] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has Z^2 is C-H.

[00155] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has R^1 is optionally substituted heteroaryl.

[00156] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has the optionally substituted heteroaryl is an optionally substituted pyridyl.

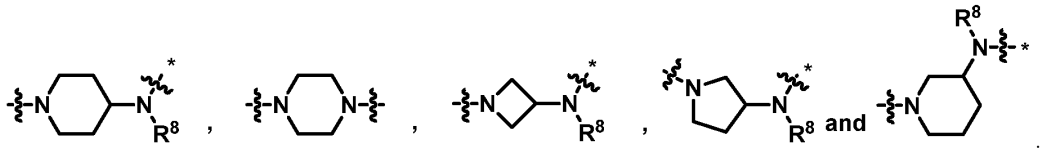
[00157] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has R^2 is optionally substituted heteroaryl.

[00158] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has R^2 is optionally substituted pyridyl.

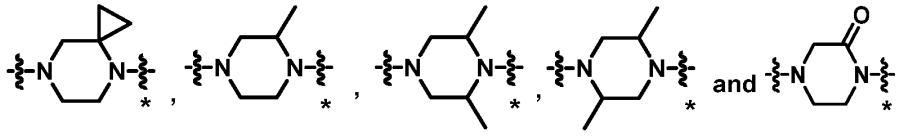
[00159] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has R^5 and R^6 are hydrogen.

[00160] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has R^5 and R^6 together form an oxo.

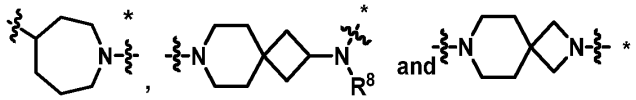
[00161] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has L is selected from:



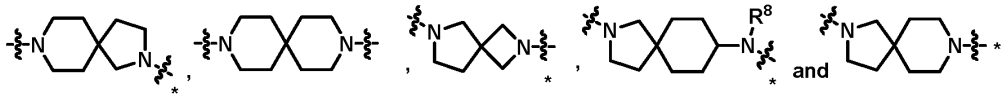
[00162] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has L is selected from:



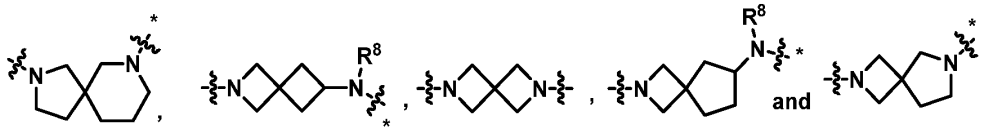
[00163] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has L is selected from:



[00164] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has L is selected from:



[00165] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has L is selected from:

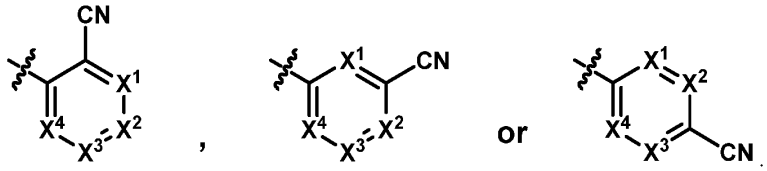


[00166] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has R^8 is hydrogen or optionally substituted C1-C6 alkyl.

[00167] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has q is 0.

[00168] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has q is 1.

[00169] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has Ar is:



[00170] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has X^1 is N.

[00171] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has X^2 is N.

[00172] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has X^3 is C-H and X^4 is C-H.

[00173] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has Z^1 is N; Z^2 is C-H; R^1 is optionally substituted pyridyl; and R^2 is optionally substituted pyridyl.

[00174] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has q is 0; and R^5 and R^6 are hydrogen.

[00175] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has q is 0; and R^5 and R^6 are hydrogen.

[00176] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has X^1 is N; X^2 is N; X^3 is C-H; and X^4 is C-H.

[00177] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has X^1 is N; X^2 is N; X^3 is C-H; and X^4 is C-H.

[00178] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has X^1 is N; X^2 is N; X^3 is C-H; and X^4 is C-H.

[00179] Another embodiment provides the method, wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, has X^1 is N; X^2 is N; X^3 is C-H; and X^4 is C-H.

[00180] One embodiment provides the method wherein the cancer is breast cancer. Another embodiment provides the method wherein the cancer is a hormone receptor positive (HR+) breast cancer. Another embodiment provides the method wherein the cancer is a human epidermal growth factor receptor 2 negative (HER2-) breast cancer. Another embodiment provides the method wherein the cancer is a HR+/HER2- breast cancer. Another embodiment provides the method wherein the cancer is a HR+/HER2-low breast cancer. Another embodiment provides the method wherein the cancer is a HR+/HER2+ breast cancer.

[00181] Another embodiment provides the method wherein the cancer is a triple negative breast cancer (TNBC). Another embodiment provides the method wherein the cancer is an invasive breast cancer. Another embodiment provides the method wherein the patient has shown progression on at least one CDK4/6 inhibitor. Another embodiment provides the method wherein the patient has shown progression on at least one endocrine-based regimen.

[00182] One embodiment provides the method wherein the cancer is uterine cancer. Another embodiment provides the method wherein the cancer is uterine sarcoma. Another embodiment provides the method wherein the cancer is endometrial cancer. Another embodiment provides the method wherein the cancer is Type I endometrial cancer.

[00183] One embodiment provides the method wherein the cancer is Type II endometrial cancer.

[00184] Another embodiment provides the method wherein the cancer is Type II endometrial papillary serous carcinoma. Another embodiment provides the method wherein the cancer is Type II endometrial clear cell carcinoma. Another embodiment provides the method wherein the cancer is Type II endometrial undifferentiated carcinoma. Another embodiment provides the method wherein the cancer is Type II endometrioid carcinoma. Another embodiment provides the method wherein the cancer is microsatellite instability (MSI) high and/or DNA mismatch repair (MMR) deficient. Another embodiment provides the method wherein the cancer is tumor mutational burden (TMB) high. Another embodiment provides the method wherein the cancer is HER2-.

[00185] One embodiment provides the method wherein the cancer is cervical cancer. Another embodiment provides the method wherein the cancer is a cervical squamous cell carcinoma.

[00186] Another embodiment provides the method wherein the cancer is a cervical adenocarcinoma.

[00187] One embodiment provides the method wherein the cancer is prostate cancer. Another embodiment provides the method wherein the cancer is prostate adenocarcinoma.

[00188] Another embodiment provides the method wherein the cancer is prostate neuroendocrine cancer. Another embodiment provides the method wherein the cancer is prostate small cell neuroendocrine cancer. Another embodiment provides the method wherein the cancer is prostate large cell carcinoma. Another embodiment provides the method wherein the cancer is prostate transitional cell carcinoma. Another embodiment provides the method wherein the cancer is prostate sarcoma.

[00189] One embodiment provides the method wherein the cancer is bladder cancer. Another embodiment provides the method wherein the cancer is urothelial cancer. Another embodiment provides the method wherein the cancer is squamous cell cancer of the bladder. Another embodiment provides the method wherein the cancer is small cell cancer of the bladder. Another embodiment provides the method wherein the cancer is adenocarcinoma of the bladder.

[00190] One embodiment provides the method wherein the cancer is lung cancer.

[00191] One embodiment provides the method wherein the cancer is non-small cell lung cancer.

[00192] One embodiment provides the method wherein the cancer is non-squamous non-small cell lung cancer.

[00193] One embodiment provides the method wherein the cancer is squamous non-small cell lung cancer.

[00194] One embodiment provides the method wherein the cancer is colon cancer.

[00195] One embodiment provides the method wherein the cancer is anal cancer.

[00196] One embodiment provides the method wherein the cancer is a meningioma.

[00197] One embodiment provides the method wherein the cancer is a glioma.

[00198] One embodiment provides the method wherein the cancer is pancreatic cancer. Another embodiment provides the method wherein the cancer is exocrine pancreatic cancer. Another embodiment provides the method wherein the cancer is neuroendocrine pancreatic cancer.

[00199] One embodiment provides the method wherein the cancer is thyroid cancer.

[00200] One embodiment provides the method wherein the cancer is sarcoma. Another embodiment provides the method wherein the cancer is soft tissue sarcoma. Another embodiment provides the method wherein the cancer is liposarcoma. Another embodiment provides the method wherein the cancer is angiosarcoma. Another embodiment provides the

method wherein the cancer is osteosarcoma. Another embodiment provides the method wherein the cancer is leiomyosarcoma. Another embodiment provides the method wherein the cancer is rhabdomyosarcoma. Another embodiment provides the method wherein the cancer is myxofibrosarcoma.

[00201] One embodiment provides the method wherein the cancer is parotid gland cancer.

[00202] One embodiment provides the method wherein the cancer is esophageal cancer.

[00203] One embodiment provides the method wherein the cancer is stomach cancer.

[00204] One embodiment provides the method wherein the cancer is skin cancer. Another embodiment provides the method wherein the cancer is nonmelanoma skin cancer. Another embodiment provides the method wherein the cancer is squamous nonmelanoma skin cancer. Another embodiment provides the method wherein the cancer is non-squamous nonmelanoma skin cancer.

[00205] One embodiment provides the method wherein the cancer is ovarian cancer. Another embodiment provides the method wherein the cancer is epithelial ovarian cancer. Another embodiment provides the method wherein the cancer is serous epithelial ovarian cancer. Another embodiment provides the method wherein the cancer is endometrioid ovarian cancer. Another embodiment provides the method wherein the cancer is clear cell ovarian cancer. Another embodiment provides the method wherein the cancer is mucinous ovarian cancer.

[00206] One embodiment provides the method wherein the cancer is adenoid cystic carcinoma.

[00207] One embodiment provides the method wherein the cancer is renal cell cancer.

[00208] One embodiment provides the method wherein the cancer is appendix cancer.

[00209] One embodiment provides the method wherein the cancer is multiple myeloma.

[00210] One embodiment provides the method wherein the cancer is acute myeloid leukemia.

[00211] One embodiment provides the method wherein the cancer is cancer of unknown primary.

[00212] One embodiment provides the method wherein the cancer is locally advanced.

[00213] One embodiment provides the method wherein the cancer is metastatic.

[00214] One embodiment provides the method wherein the method is adjuvant therapy following surgical resection.

[00215] One embodiment provides the method wherein the method is neo-adjuvant therapy.

[00216] One embodiment provides the method wherein the method is first-line systemic therapy for locally advanced or metastatic disease.

[00217] One embodiment provides the method wherein the patient has relapsed after prior therapy.

[00218] One embodiment provides the method wherein the patient has acquired resistance to prior therapy.

[00219] One embodiment provides the method wherein the patient is refractory to therapy.

[00220] One embodiment provides the method wherein the patient has shown progression on cytotoxic chemotherapy.

[00221] One embodiment provides the method wherein the cancer is characterized by existence of AKT1-E17K mutation.

[00222] One embodiment provides the method wherein the cancer exhibits one or more co-occurring alterations selected from a PIK3CA alteration, a PIK3R1 alteration, an AKT1 alteration, and PTEN alteration.

[00223] One embodiment provides the method wherein the patient exhibits risk factors for hyperglycemia.

[00224] One embodiment provides the method wherein the patient exhibits risk factors selected from obesity, body mass index greater than or equal to 30, fasting blood glucose over 160 mg/dL, HbA1c greater than 6.0.

[00225] One embodiment provides the method wherein the patient exhibits Type I diabetes, diabetes requiring insulin, diabetes requiring metformin or another oral hypoglycemic agent, or pre-diabetes treated with metformin or another oral hypoglycemic agent.

[00226] Another embodiment provides the method wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, is selected from the group consisting of:

6-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)nicotinonitrile;

6-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)nicotinonitrile;

6-((1-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)nicotinonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)picolinonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)isonicotinonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)nicotinonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)picolinonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)isonicotinonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)nicotinonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)picolinonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)isonicotinonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)oxy)nicotinonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)picolinonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)picolinonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)picolinonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)nicotinonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)isonicotinonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrazine-2-carbonitrile;

2-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyridazine-4-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanoisonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-6-cyanonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-5-cyanopicolinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-5-cyanonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-3-cyanopicolinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-4-cyanonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-6-cyanopicolinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-4-cyanopicolinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanopyrimidine-4-carboxamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-6-cyanopyrimidine-4-carboxamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanobenzo[d]thiazole-5-carboxamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyano-5-fluorobenzo[d]thiazole-7-carboxamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-3-cyanoisonicotinamide;

N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(2-cyanopyridin-4-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(6-cyanopyridin-3-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(6-cyanopyridin-2-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(6-cyanopyrazin-2-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(6-cyanopyrimidin-4-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(2-cyanopyrimidin-5-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(6-cyanopyridazin-4-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(2-cyanopyrimidin-4-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(5-cyanopyridazin-3-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-(4-cyanopyrimidin-2-yl)piperazin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyridazine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyridazine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyridazine-4-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanoisonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-6-cyanopicolinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-5-cyanonicotinamide;

N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-3-cyanoisonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-4-cyanonicotinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-3-cyanopicolinamide;
4-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)picolinonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)picolinonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)nicotinonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)isonicotinonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrazine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyridazine-3-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-3-cyanopyridazine-4-carboxamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyrimidine-5-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-5-cyanopyrimidine-4-carboxamide;
5-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)nicotinonitrile;

2-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)isonicotinonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrazine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-5-cyanopicolinamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)picolinonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)picolinonitrile;
5-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)picolinonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)picolinonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)picolinonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)isonicotinonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrazine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
5-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)nicotinonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)picolinonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanoisonicotinamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyrimidine-4-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-6-cyanopyrimidine-4-carboxamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)isonicotinonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyrimidine-2-carbonitrile;

6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
3-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
3-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)isonicotinonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)isonicotinonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-4-cyanopicolinamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanopyrimidine-4-carboxamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyrimidine-2-carbonitrile;
3-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)nicotinonitrile;
3-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)isonicotinonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl)amino)pyrimidine-2-carbonitrile;
5-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)picolinonitrile;
5-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyridazine-3-carbonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyridazine-3-carbonitrile;
3-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyrazine-2-carbonitrile;

3-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)pyrazine-2-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-6-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-6-cyanonicotinamide;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-6-cyanonicotinamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)picolinonitrile;
7-(4-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)-5-fluorobenzo[d]thiazole-2-carbonitrile;
7-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)-5-fluorobenzo[d]thiazole-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)-6-fluorobenzo[d]thiazole-2-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyano-5-fluorobenzo[d]thiazole-7-carboxamide;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyano-6-fluorobenzo[d]thiazole-4-carboxamide;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)benzo[d]thiazole-2-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyanobenzo[d]thiazole-5-carboxamide;
4-((2S,6S)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-2-carbonitrile;
2-((2S,6S)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-4-carbonitrile;
6-((2S,6S)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-4-carbonitrile;
4-((2R,6R)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-2-carbonitrile;
2-((2R,6R)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-4-carbonitrile;

6-((2R,6R)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-4-carbonitrile;
4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)pyrimidine-2-carbonitrile;
2-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)pyrimidine-4-carbonitrile;
6-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)pyrimidine-4-carbonitrile;
4-((3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3-azabicyclo[3.2.1]octan-8-yl)amino)pyrimidine-2-carbonitrile;
6-((3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3-azabicyclo[3.2.1]octan-8-yl)amino)pyrimidine-4-carbonitrile;
4-(3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrimidine-2-carbonitrile;
2-(3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrimidine-4-carbonitrile;
6-(3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrimidine-4-carbonitrile;
(S)-4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)pyrimidine-2-carbonitrile;
(S)-2-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)pyrimidine-4-carbonitrile;
(S)-6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)pyrimidine-4-carbonitrile;
4-(8-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidine-2-carbonitrile;
2-(8-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidine-4-carbonitrile;
6-(8-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-1,4-diazepan-1-yl)pyrimidine-2-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-1,4-diazepan-1-yl)pyrimidine-4-carbonitrile;

4-((1R,4R)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-2-carbonitrile;
2-((1R,4R)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-4-carbonitrile;
6-((1R,4R)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-4-carbonitrile;
4-(5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimidine-2-carbonitrile;
2-(5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimidine-4-carbonitrile;
6-(5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimidine-4-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl)amino)-1,3,5-triazine-2-carbonitrile;
(S)-4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-3-yl)amino)-1,3,5-triazine-2-carbonitrile;
(R)-4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)pyrimidine-2-carbonitrile;
(R)-2-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)pyrimidine-4-carbonitrile;
(R)-6-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)pyrimidine-4-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-1,4-diazepan-1-yl)pyrimidine-4-carbonitrile;
N-(3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3-azabicyclo[3.2.1]octan-8-yl)-2-cyanopyrimidine-4-carboxamide;
N-(3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3-azabicyclo[3.2.1]octan-8-yl)-6-cyanopyrimidine-4-carboxamide;
2-((3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3-azabicyclo[3.2.1]octan-8-yl)amino)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl-d3)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl-d3)amino)-1,3,5-triazine-2-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyano-N-(methyl-d3)pyrimidine-4-carboxamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(6-oxo-1,6-dihydropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)thiazole-2-carbonitrile;
4-((7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-7-azaspiro[3.5]nonan-2-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[3.5]nonan-2-yl)-1,3,5-triazine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-1,4-diazepan-1-yl)-1,3,5-triazine-2-carbonitrile;
4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[4.4]nonan-2-yl)-1,3,5-triazine-2-carbonitrile;
4-(2-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,8-diazaspiro[4.5]decan-8-yl)-1,3,5-triazine-2-carbonitrile;

4-(2-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[4.5]decan-7-yl)-1,3,5-triazine-2-carbonitrile;
4-(9-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,9-diazaspiro[5.5]undecan-2-yl)-1,3,5-triazine-2-carbonitrile;
(R)-4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[4.4]nonan-2-yl)-1,3,5-triazine-2-carbonitrile;
4-((2R,6R)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-(5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-1,3,5-triazine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-oxo-1,2-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-cyclobutyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(cyclohex-1-en-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-cyclohexyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-oxo-1,6-dihydropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(2-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[3.5]nonan-7-yl)-1,3,5-triazine-2-carbonitrile;
(S)-4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[4.4]nonan-2-yl)-1,3,5-triazine-2-carbonitrile;

4-(3-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-1,3,5-triazine-2-carbonitrile;
4-(8-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,3,5-triazine-2-carbonitrile;
4-((1R,4R)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-1,3,5-triazine-2-carbonitrile;
(R)-4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
(S)-4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-((2S,6S)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)-1,3,5-triazine-2-carbonitrile;
4-((2R,6S)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)azepan-4-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-((4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-1,4-oxazepan-6-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-methyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-(8-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,3,5-triazine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-isopropyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-methoxy-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine-5-carboxamide;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-N,N-dimethyl-3H-imidazo[4,5-b]pyridine-5-carboxamide;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(tetrahydro-2H-pyran-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)azetidin-3-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-(6-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-diazaspiro[3.4]octan-2-yl)-1,3,5-triazine-2-carbonitrile;
4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-2-carbonitrile;
4-(6-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-1,3,5-triazine-2-carbonitrile;

4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
5-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazine-1-carbonyl)thiazole-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(cyclohex-1-en-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3,6-dihydro-2H-pyran-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(6-oxo-1,6-dihydropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-(6-oxo-1,6-dihydropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyanophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
N-(1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)-2-cyano-N-methylpyrimidine-4-carboxamide;
(R)-4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-3-yl)amino)-1,3,5-triazine-2-carbonitrile;

4-((1S,4S)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-1,3,5-triazine-2-carbonitrile;
4-((3aR,6aS)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidine-2-carbonitrile;
4-((3aR,6aS)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,5-triazine-2-carbonitrile;
4-((3aR,6aR)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-methyl-5-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methyl-5-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(4-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
4-(7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidine-2-carbonitrile;
4-((7-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-7-azaspiro[3.5]nonan-2-yl)amino)pyrimidine-2-carbonitrile;
4-(8-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,8-diazaspiro[4.5]decan-2-yl)-1,3,5-triazine-2-carbonitrile;
4-(9-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,9-diazaspiro[5.5]undecan-3-yl)pyrimidine-2-carbonitrile;
4-(9-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,9-diazaspiro[5.5]undecan-3-yl)-1,3,5-triazine-2-carbonitrile;
4-(6-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidine-2-carbonitrile;
4-((3aS,6aS)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)-1,3,5-triazine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;

2-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
6-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-4-carbonitrile;
6-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-4-carbonitrile;
4-((1S,4S)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-2-carbonitrile;
6-((1S,4S)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-4-carbonitrile;
2-((1S,4S)-5-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-4-carbonitrile;
4-((2S,6R)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-2-carbonitrile;
2-((2S,6R)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-4-carbonitrile;
6-((2S,6R)-4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)pyrimidine-4-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-oxo-1,2-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-cyanopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-cyanopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(4-methyl-3-oxo-1,4-diazepan-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-oxomorpholino)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-cyclopentyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(dimethylamino)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-4-methylpiperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-methoxyphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(tert-butyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-N-methyl-3H-imidazo[4,5-b]pyridine-5-carboxamide;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-cyanopyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-cyanopyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-fluoro-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-6-fluoro-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-oxooxazolidin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-fluoropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-chloro-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine-5-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(3-cyanopyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-cyanopyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyanopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine-6-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-1-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
methyl 2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(fluoromethoxy)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(tetrahydrofuran-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-cyanopyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-cyanopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(oxetan-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methoxyphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(trifluoromethoxy)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyanopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-isopropoxy-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((4-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(methoxy-d3)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-cyanopyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyanopyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-cyanopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(4-(4-(2-(2-aminopyridin-3-yl)-5-(pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperazin-1-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(pyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((7-(4-(2-(2-aminopyridin-3-yl)-5-morpholino-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-7-azaspiro[3.5]nonan-2-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(methylthio)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(methylsulfonyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-1H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluoro-3-methoxyphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)acetamide;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl-d3)amino)pyrimidine-2-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)(methyl-d3)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)azetidin-3-yl)amino)pyrimidine-2-carbonitrile;
4-((7-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-7-azaspiro[3.5]nonan-2-yl)amino)pyrimidine-2-carbonitrile;
4-((2-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-azaspiro[3.3]heptan-6-yl)amino)pyrimidine-2-carbonitrile;
4-((2-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2-azaspiro[3.5]nonan-7-yl)amino)pyrimidine-2-carbonitrile;
4-(6-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidine-2-carbonitrile;
4-(8-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidine-2-carbonitrile;
4-((3aR,6aS)-5-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidine-2-carbonitrile;
4-((3aS,6aS)-5-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl-4-d)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl-4-d)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(cyclopent-1-en-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-vinyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl-d3)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(bis(methyl-d3)amino)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-((methyl-d3)amino)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(azetidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(isoxazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(oxazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methylisoxazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-methylisoxazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-methyl-1H-pyrazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-ethyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-1H-pyrazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-(2-oxopyrrolidin-1-yl)phenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluoro-2-methoxyphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-(trifluoromethyl)phenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-(trifluoromethyl)phenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3,5-dimethylisoxazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-(difluoromethyl)-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2,4-difluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-methoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methylpyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methylpyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-isopropyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(isothiazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-cyano-1-methyl-1H-pyrrol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(thiazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(isothiazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1,5-dimethyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-bromo-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-5-bromo-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)-1,3,5-triazine-2-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)(methyl)amino)pyrimidine-2-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-(7-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidine-2-carbonitrile;
4-(2-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-2,7-diazaspiro[3.5]nonan-7-yl)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(methylsulfinyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(8-(2-aminopyridin-3-yl)-6-hydroxy-9H-purin-9-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-hydroxy-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(5-amino-2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-chloro-4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-6-methyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-1-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole-6-carbonitrile;
2-(2-aminopyridin-3-yl)-1-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole-5-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)(methyl-d3)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl-4-d)amino)pyrimidine-2-carbonitrile;
4-((1-((4-(2-(2-aminopyridin-3-yl)-5,6-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)phenyl)methyl-d2)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(8-(2-aminopyridin-3-yl)-9H-purin-9-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
(S)-4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(tetrahydrofuran-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
(R)-4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(tetrahydrofuran-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(hydroxymethyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(fluoromethyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(pyrrolidin-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methoxypyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-ethynyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)-N-methylacetamide;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-methoxypyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(5-(3-aminophenyl)-2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
N-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)isobutyramide;
N-(3-(3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-2-(2-isobutyramidopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)isobutyramide;
methyl (3-(2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)carbamate;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-(dimethylamino)phenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
N-(1-(3-(2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)piperidin-4-yl)-N-methylacetamide;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluoro-2-methylphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)-5-fluorobenzamide;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyano-4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluoro-2-(trifluoromethyl)phenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(o-tolyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(m-tolyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(p-tolyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-(trifluoromethyl)phenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
isopropyl 2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate;
4-((1-(4-(2-(2-aminopyridin-3-yl)-1H-benzo[d]imidazol-1-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-1H-imidazo[4,5-b]pyridin-1-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-methylpyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(difluoromethoxy)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-hydroxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1,3-dimethyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-1H-imidazo[4,5-c]pyridin-1-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)(methyl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-(difluoromethoxy)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-(difluoromethoxy)pyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluoro-2-hydroxyphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluoro-3-hydroxyphenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-1H-imidazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-cyanopyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-6-bromo-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-5-methyl-3H-imidazo[4,5-b]pyridine-6-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluoropyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-1-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-1H-imidazo[4,5-c]pyridine-6-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methyloxazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-cyclopropyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-1-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-1H-imidazo[4,5-b]pyrazine-5,6-dicarbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridine-6-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluoropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-1H-1,2,4-triazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-ethoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-fluoropyridin-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-methyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-methoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-1H-1,2,3-triazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-6-methyl-3H-imidazo[4,5-b]pyridine-5-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-methyl-1H-1,2,4-triazol-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methyl-2H-1,2,3-triazol-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methyl-4H-1,2,4-triazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-(difluoromethyl)-1H-1,2,4-triazol-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(4-aminopyrimidin-5-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(5-(5-fluoropyridin-2-yl)-2-(pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminophenyl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(5-(5-fluoropyridin-2-yl)-2-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-(methoxy-d3)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-(difluoromethoxy)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-(fluoromethoxy)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methoxypyrimidin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methylpyrazin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methoxypyrazin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-ethoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-cyclopropoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-isopropoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-cyclopropylpyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-methyl-4H-1,2,4-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(3-methyl-1H-1,2,4-triazol-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1H-1,2,4-triazol-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1H-1,2,3-triazol-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2H-1,2,3-triazol-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methyl-1H-1,2,3-triazol-1-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(oxazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluoropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-(methoxy-d3)pyridin-3-yl-2-d)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-(methoxy-d3)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-5-hydroxy-3H-imidazo[4,5-b]pyridine-6-carbonitrile;
4-((1-(4-(2-(2-amino-4-fluoropyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(5-(5-fluoropyridin-2-yl)-2-(pyrimidin-5-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-6-(5-fluoropyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyrimidin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-methylpyrimidin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyrazin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-(fluoromethoxy)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-(fluoromethyl)-6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-(methyl-d3)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-ethyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-isopropyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-isopropyl-1H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methyl-5-(methyl-d3)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methyl-2H-1,2,3-triazol-4-yl-5-d)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-(difluoromethyl)-6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-(fluoromethyl)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-(fluoromethyl)-1H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-(methyl-d3)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminoisoxazol-4-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-(fluoromethoxy-d2)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-(fluoromethyl-d2)-6-oxo-1,6-dihydropyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-(cyanomethyl)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-(fluoromethyl)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(1-(fluoromethyl)-1H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-ethyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-isopropyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-(cyanomethyl)-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(4-(2-(3-aminopyrazin-2-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)-2H-1,2,3-triazol-2-yl)acetamide;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2-methyl-2H-1,2,3-triazol-4-yl-5-d)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(6-methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(6-(methoxy-d3)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(5-(methoxy-d3)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(6-(fluoromethoxy)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(3-aminopyrazin-2-yl)-5-(6-(fluoromethoxy-d2)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-cyclopropoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-isopropoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-isopropylpyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;

4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-cyclopropylpyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-(difluoromethyl)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-ethylpyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-(fluoromethyl)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-(difluoromethyl)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile; and
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-(trifluoromethyl)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile.

[00227] Another embodiment provides the method wherein the compound of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, is selected from the group consisting of:
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(4-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
2-(2-aminopyridin-3-yl)-3-(4-((4-((2-cyanopyrimidin-4-yl)amino)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine-6-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(2-methyl-2H-1,2,3-triazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(6-methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile;
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-(difluoromethoxy)pyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile; and
4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-cyclopropoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile.

Pharmaceutical Compositions

[00228] In certain embodiments, the heterocyclic AKT1 inhibitor Compound 1, or pharmaceutically acceptable salt or solvate thereof, is administered as a pure chemical. In

other embodiments, the heterocyclic AKT1 inhibitor Compound 1, or pharmaceutically acceptable salt or solvate thereof, is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable or acceptable excipient, a physiologically suitable or acceptable excipient, or a physiologically suitable or acceptable carrier) selected based on a chosen route of administration and standard pharmaceutical practice.

[00229] Provided herein is the method wherein the pharmaceutical composition comprising the heterocyclic AKT1 inhibitor Compound 1, or pharmaceutically acceptable salt or solvate thereof is administered orally. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. In some embodiments, suitable nontoxic solid carriers are used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (*See*, *e.g.*, *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00230] Provided herein is the method wherein the pharmaceutical composition is administered by injection. In some embodiments, the heterocyclic AKT1 inhibitor Compound 1, or pharmaceutically acceptable salt or solvate thereof, is formulated for administration by injection. In some instances, the injection formulation is an aqueous formulation. In some instances, the injection formulation is a non-aqueous formulation. In some instances, the injection formulation is an oil-based formulation, such as sesame oil, or the like.

[00231] The dose of the composition comprising the heterocyclic AKT1 inhibitor Compound 1, or pharmaceutically acceptable salt or solvate thereof, differs depending upon the subject or patient's (e.g., human) condition. In some embodiments, such factors include general health status, age, and other factors. Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models

and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00232] In certain embodiments, the heterocyclic AKT1 inhibitor of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, is administered as a pure chemical. In other embodiments, the heterocyclic AKT1 inhibitor of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable or acceptable excipient, a physiologically suitable or acceptable excipient, or a physiologically suitable or acceptable carrier) selected based on a chosen route of administration and standard pharmaceutical practice.

[00233] Provided herein is the method wherein the pharmaceutical composition comprising the heterocyclic AKT1 inhibitor of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof is administered orally. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. In some embodiments, suitable nontoxic solid carriers are used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (*See*, *e.g.*, *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00234] Provided herein is the method wherein the pharmaceutical composition is administered by injection. In some embodiments, the heterocyclic AKT1 inhibitor of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, is formulated for administration by injection. In some instances, the injection formulation is an aqueous formulation. In some instances, the injection formulation is a non-aqueous formulation. In some instances, the injection formulation is an oil-based formulation, such as sesame oil, or the like.

[00235] The dose of the composition comprising the heterocyclic AKT1 inhibitor of Formula (Ib), or pharmaceutically acceptable salt or solvate thereof, differs depending upon the subject or patient's (e.g., human) condition. In some embodiments, such factors include general health status, age, and other factors. Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic

and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

EXAMPLES

[00236] The following illustrative examples are representative of embodiments of the software applications, systems, and methods described herein and are not meant to be limiting in any way.

Example 1: Kinase Inhibitory Activity of Compound 1 *in vitro*

[00237] Compound 1 was tested in biochemical assays to assess activity against kinase family members in multiple independent experiments.

[00238] Biochemical activity of Compound 1 was assessed through *in vitro* profiling of a kinase panel; experiments were performed at Reaction Biology Corporation using the "HotSpot" assay platform. Briefly, specific kinase/substrate pairs, along with required cofactors, were prepared in reaction buffer containing 20 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na_3VO_4, 2 mM DTT, and 1% DMSO. Following kinase incorporation into the solution, Compound 1 was added in 10-point, 3-fold dose curves starting at a 10 μM, 3 μM or 1 μM as the highest concentration. After a 20-minute pre-incubation, a mixture of ATP and ^{33}P-ATP to a final concentration of 10 μM was added into the reaction mixture. Following the addition of ATP and ^{33}P-ATP, reactions were incubated at room temperature for 120 minutes. Kinase activity was detected by the P81 filter-binding method: after incubation, reaction mixture was spotted onto P81 ion exchange filter paper (Whatman). Unbound phosphate was removed by extensive washing of filters in 0.75% phosphoric acid. After subtraction of background derived from control reactions containing inactive enzyme, kinase activity data was expressed as the percent remaining kinase activity in test samples compared to vehicle (dimethyl sulfoxide) reactions (see **Table 1**).

Table 1. Kinase panel

Kinase	**% Inhibition 1 μM**
MELK	80.9%
AKT1	78.6%
AKT2	74.1%

TNIK	68.6%
AKT3	67.5%
DYRK3	64.3%
HASPIN	49.7%

[00239] Half-maximal inhibitory concentration (IC50) values were calculated using the inhibition of conversion ratio using Dotmatics Knowledge Solutions Studies curve fitting (fitting software: Dotmatics, Bishops Stortford, UK, CM23) and are provided in **Table 2**.

[00240] Biochemical assays tested Compound 1 potency against kinase family members. **Table 1** lists the mean kinase activity (e.g., percent remaining kinase activity in test samples compared to vehicle). Out of a total of 370 enzymes tested, only 6 were inhibited >50% in the presence of 1 μM of Compound 1. Of the 6 enzymes with >50% inhibition, MELK showed the highest affect, with >80% inhibition. **Table 2** lists the mean potency (IC50) of Compound 1 inhibition against the enzymes. MELK, DYRK3, AKT1, AKT3, and AKT2 demonstrated potencies ranging from between 293 nM and 749 nM.

Table 2. Kinase panel potency

Kinase	**IC50 (nM)**
AKT3	749
DYRK3	648
AKT1	607
AKT2	566
MELK	293

Example 2: Target Engagement of Compound 1 *in vivo*

[00241] Target engagement was measured using NanoBRET™, a bioluminescence resonance energy transfer (BRET)-based assay using NanoLuc® luciferase. The assay measures compound binding at select target proteins fused to NanoLuc® luciferase in human embryonic kidney (HEK)-293 cells. HEK-293 cells were allowed to reach 80-90% confluence before detaching and splitting. The cultivated HEK-293 cells were transfected with NanoLuc-tagged proteins using ratios of 9.0 μg/mL of transfection carrier DNA, 1.0 μg/mL of NanoLuc® fusion vector DNA, and 1 mL of Opti-MEM Reduced Serum Medium (phenol red free). The solution was mixed thoroughly. In a sterile conical tube, 1 part

lipid:DNA complex was mixed with 20 parts HEK-293 cells in suspension. The HEK-293 cells and the lipid:DNA complex were dispensed into a sterile tissue-culture treated 384 well assay plate and incubated for 20 to 30 hours. A 3-fold, 10-point dilution of Compound 1 was performed with DMSO. Cell plates were removed from the incubator, and the serial dilution of Compound 1 was transferred; the DMSO concentration was consistent at 0.1% in all wells. Plates were incubated for 2 hours. NanoBRET™ kinase tracer was prepared and transferred into the 384 well plate wells. Plates were incubated at 37°C and 5% CO_2 for 2 hours. A complete substrate plus inhibitor solution was prepared in Opti-MEM Reduced Serum Medium (phenol red free) and added to the 384 well plates. Plates were incubated at room temperature. BRET measurement was performed using a microplate reader, and BRET ratios (Acceptor sample / Donor sample × 1000) were calculated for each measured well of the plate. The half maximal effective concentration (EC50) values were calculated using a four-parameter fit model using Dotmatics Knowledge Solutions Studies curve fitting software (Dotmatics, Bishops Stortford, UK, CM23). In HEK-293 cells, it was determined that Compound 1 engages AKT1-E17K at an EC50 of 7.01 nM, as shown in **Table 3**.

Table 3. Target engagement

Target	**EC50 (nM)**	**SEM**	**N**
AKT1-E17K	7.01	0.67	14

Example 3: pAKT Homogeneous Time Resolved Fluorescence Assay for Determining the effect of Compound 1 on Cellular PI3K/AKT Pathway Signaling

[00242] AKT phosphorylation was measured using homogeneous time resolved fluorescence (HTRF®). The Phospho-AKT1/2/3(Ser473) HTRF® assay measures AKT phosphorylation on Ser473 across all isoforms, as a readout of AKT/PI3K pathway signaling. Briefly, cells from a human papillary thyroid carcinoma cell line harboring an AKT1 E17K mutation (IHH-4 cells) or a human hepatocellular carcinoma cell line containing the wild-type (WT) AKT1 (HepG2/C3 cells) were seeded at 16,000 cells/well in 24 µL growth media in a 384-well plate and allowed to adhere at 37° C with 5% CO_2 overnight. The following day, compounds were serially diluted into 10-point, 3-fold dilution curves in 384-well plates. Compound 1 was transferred to cell plates such that the final concentration range was 0.508 nM to 10 µM in 0.1% DMSO with 0.1% DMSO being used as negative control. Cells were incubated with Compound 1 for 1 hour at 37° C with 5% CO_2. Cells were lysed by addition

of 8 µL 4x lysis buffer provided with HTRF® kit plus 1x protease/phosphatase inhibitor cocktail. A 4 µL volume of Advanced Phospho-AKT1/2/3(Ser473) d2 antibody working solution and 4 µL of Advanced Phospho-AKT1/2/3(Ser473) Europium Cryptate antibody working solution (prepared in the detection buffer) were added to each lysed well. The plates were incubated overnight at room temperature before measuring the HTRF® readout. A 25 µL volume of the mix was transferred from the cell plate to a reader plate and the HTRF® readout was measured using standard HTRF® settings. EC50 values were calculated using a four-parameter fit model using Dotmatics Knowledge Solutions Studies curve fitting software (Dotmatics, Bishops Stortford, UK, CM23) and are provided in **Table 4**.

[00243] In HepG2/C3 cells (e.g., AKT1-WT) it was determined that Compound 1 inhibits AKT1 p-S473 pathway signaling at an EC50 of 111.7 nM. Conversely, in IHH-4 cells (*e.g.*, AKT1-E17K) Compound 1 was shown to inhibit AKT1 p-S473 pathway signaling at an EC50 of 10.5 nM, thus demonstrating 10.6x selectivity against AKT1-E17K over AKT1-WT cells (as shown in **Table 4**).

Table 4. Pathway selectivity

Cell line	AKT1 mut	EC50 (nM)	SEM	N
IHH-4	E17K	10.5	0.9	27
HepG2/C3	WT	111.7	8.3	12

Example 4: CellTiter-Glo® Assay for Determining the effect of Compound 1 on Cellular Proliferation

[00244] The effects of Compound 1 on cell proliferation were measured using CellTiter-Glo® cell viability assay (CTG) in Ba/F3 parental cells and those containing various AKT alterations (e.g., AKT1-E17K, AKT1-D323H, and AKT2-E17K). Cells were prepared with a 90 µL volume of cell suspension added to each well of a 96-well plate to obtain a final cell density of 3.0×10^3 cells/well. Plates were incubated in a humidified incubator at 37°C and 5% CO_2. Compound 1 was dissolved in DMSO to create a 10 mM stock solution. Compound 1 or reference control solution was prepared with DMSO and dispensed to each well (triplicate for each concentration) of the cell plates, yielding 9 concentrations of Compound 1 from 0.30 to 10000 nM with a final DMSO concentration of 0.1%. Cell plates were cultured for 3 days. On Day 3, CellTiter-Glo® reagent was thawed and cell plates were equilibrated at room temperature for approximately 30 minutes. A 100 µL volume of CellTiter-Glo® reagent was then added to each well, which was equal to the volume of cell culture medium

present in each well. Contents were mixed for 5 minutes on an orbital shaker to induce cell lysis. Cell plates were allowed to incubate at room temperature for 20 minutes to stabilize the luminescent signal. Luminescence was then recorded using a microplate reader. EC50 values were calculated using a four-parameter fit model using Dotmatics Knowledge Solutions Studies curve fitting software (Dotmatics, Bishops Stortford, UK, CM23) and are provided in **Table 5**.

[00245] In Ba/F3 cells harboring an AKT1-E17K mutation Compound 1 was shown to inhibit cell growth at an EC50 of 9.79 nM. In Ba/F3 cells harboring an AKT1-D323H mutation (e.g., an AKT1 mutation outside the allosteric binding site that drives IL-3-independent proliferation of Ba/F3 cells) Compound 1 was shown to inhibit cell growth at an EC50 of 230.3 nM. In Ba/F3 cells harboring an AKT2-E17K mutation Compound 1 was shown to inhibit cell growth at an EC50 of 2309.75 nM (as shown in **Table 5**). These results demonstrate that Compound 1 is 23.5x more selective for AKT1-E17K over AKT1-D323H. Furthermore, the results show that Compound 1 is 235.9x more selective for AKT1-E17K over AKT2-E17K.

Table 5. Cellular selectivity

Target	**Cell line**	**EC50**	**SEM**	**N**
AKT1-E17K	Ba/F3	9.79	0.8	14
AKT1-D323H	Ba/F3	230.3	30.6	11
AKT2-E17K	Ba/F3	2309.75	288.5	5
Parental	Ba/F3	>10000	NA	11

Example 5: Evaluation of the Antitumor Activity of Compound 1 in Human Breast Cancer (HR+ HER2-low) Xenograft Mouse Models

[00246] For human AKT1 E17K-mutated breast cancer (HR+ HER2-low) patient-derived xenograft (PDX) mouse models, which has low HER2 expression, administration of Compound 1 or Capivasertib started when the mean tumor volume reached approximately 130-180 mm^3, as indicated in **Figure 1A**. Animals were monitored for tumor growth, body weight changes, and general health/behavior. Mice were assigned to respective groups based on their starting tumor volume and body weight such that the average values were the same for each treatment group. The study design indicating the groups (*e.g.*, drug treatment) and number of animals per group are shown below in **Table 6** and **Table 7** (includes plasma drug concentration (AUC_{last})).

[00247] Briefly, Compound 1 or Capivasertib were dosed orally (PO) once per day (QD) in mice bearing patient derived breast cancer (HR+ HER2-low) tumor fragments. Compound 1 and Capivasertib were well-tolerated in mouse xenograft models of HR+ HER2-low mutant human breast cancer (see **Figure 1B**). Compound 1 induced tumor growth inhibition (TGI) of 109% at 10 mg/kg QD and 116% at 30 mg/kg QD (depicted in **Figure 1A**). Benchmark compound Capivasertib induced TGI of 68% at 100 mg/kg QD. As shown in **Figure 1C**, no adverse hyperglycemia was observed with Compound 1, with mean blood glucose values of 205 mg/dL at 10 mg/kg QD, and 141 mg/dL at 30 mg/kg QD. In contrast, treatment with Capivasertib resulted in mean blood glucose values of 406 mg/dL at 100 mg/kg QD one hour post final dose (see **Figure 1C**). Mean blood glucose values of 183 mg/dL for the vehicle were observed.

Table 6. Study design for breast cancer (HR+ HER2-low) PDX

Group No.	Drug	No. Animals	Dose (mg/kg)	Volume (mL/kg)	Route	Regimen	Duration
1	Vehicle	6	0	10	PO	QD	28
3	Compound 1	6	10	10	PO	QD	28
4	Compound 1	6	30	10	PO	QD	61
5	Capivasertib	6	100	10	PO	QD	28

Table 7. Study design for breast cancer (HR+ HER2-low) PDX

Group No.	Drug	Dose (mg/kg)	AUClast (h*ng/mL)
1	Vehicle	0	0
3	Compound 1	10	7070
4	Compound 1	30	26026
5	Capivasertib	100	25695

Example 6: Evaluation of the Antitumor Activity of Compound 1 in Human Endometrial Cancer Xenograft Mouse Models

[00248] For human AKT1 E17K-mutated endometrial cancer patient-derived xenograft (PDX) mouse models, administration of Compound 1 or Capivasertib started when the mean tumor volume reached approximately 130-180 mm^3, as indicated in **Figure 2A**. Animals were monitored for tumor growth, body weight changes, and general health/behavior. Mice were assigned to respective groups based on their starting tumor volume and body weight such that the average values were the same for each treatment group. The study design indicating the groups (*e.g.*, drug treatment) and number of animals per group are shown below in **Table 8** and **Table 9 (**includes plasma drug concentration (AUC_{last})).

[00249] Briefly, Compound 1 or Capivasertib were dosed orally (PO) once per day (QD) in mice bearing patient derived endometrial cancer tumor fragments. Compound 1 and Capivasertib were well-tolerated in mouse xenograft models of human endometrial cancer (see **Figure 2B**). Compound 1 induced tumor growth inhibition (TGI) of 62% at 5 mg/kg QD, 76% at 10 mg/kg QD, and 94% at 30 mg/kg QD (depicted in **Figure 2A**). Benchmark compound Capivasertib induced a TGI of 65% at 100 mg/kg twice a day (BID), with drug administered on a 4 days on/3 days off schedule. As shown in **Figure 2C**, no adverse hyperglycemia was observed with Compound 1, with mean blood glucose values of 245 mg/dL at 5 mg/kg QD group, 265 mg/dL at 10 mg/kg QD group, and 259 mg/dL at 30 mg/kg QD. In contrast, treatment with Capivasertib resulted in mean blood glucose values of 523 mg/dL at 100 mg/kg BID 4ON/3OFF one hour post final dose (see **Figure 2C**). Mean blood glucose values of 295 mg/dL for the vehicle were observed.

Table 8. Study design for endometrial cancer PDX

Group No.	**Drug**	**No. Animals**	**Dose (mg/kg)**	**Volume (mL/kg)**	**Route**	**Regimen**	**Duration**
1	Vehicle	6	0	10	PO	QD	14
2	Compound 1	6	5	10	PO	QD	14
3	Compound 1	6	10	10	PO	QD	14
4	Compound 1	6	30	10	PO	QD	14
5	Capivasertib	6	100	10	PO	BID, 4ON/3OFF	14

Table 9. Study design for endometrial cancer PDX

Group No.	**Drug**	**Dose (mg/kg)**	**AUClast (h*ng/mL)**
1	Vehicle	0	0
2	Compound 1	5	5254
3	Compound 1	10	12685
4	Compound 1	30	42924
5	Capivasertib	100	35448

Example 7: Evaluation of the Antitumor Activity of Compound 1 in Human Triple Negative Breast Cancer Xenograft Mouse Models

[00250] For human AKT1 E17K-mutated triple negative breast cancer (TNBC) patient-derived xenograft (PDX) mouse models, administration of Compound 1 or Capivasertib started when the mean tumor volume reached approximately 112-266 mm^3, as indicated in

Figure 3A. Animals were monitored for tumor growth, body weight changes, and general health/behavior. Mice were assigned to respective groups based on their starting tumor volume and body weight such that the average values were the same for each treatment group. The study design indicating the groups (*e.g.*, drug treatment) and number of animals per group are shown below in **Table 10** and **Table 11 (**includes plasma drug concentration (AUC_{last})).

[00251] Briefly, Compound 1 or Capivasertib were dosed orally (PO) once per day (QD) in mice bearing patient derived triple negative breast cancer (TNBC) tumor fragments. Compound 1 and Capivasertib were well-tolerated in mouse xenograft models of human TNBC breast cancer (see **Figure 3B**). Compound 1 induced tumor growth inhibition (TGI) of 103% at 30 mg/kg QD (depicted in **Figure 3A**). Benchmark compound Capivasertib induced a TGI of 84% at 100 mg/kg BID for 3 days, then QD for 19 days. As shown in **Figure 3C**, no adverse hyperglycemia was observed with Compound 1, with mean blood glucose values of 240 mg/dL at 30 mg/kg QD. In contrast, treatment with Capivasertib resulted in mean blood glucose values of 415 mg/dL at 100 mg/kg BIDx3, QDx19 one hour post final dose (see **Figure 3C**). Mean blood glucose values of 280 mg/dL for the vehicle were observed.

Table 10. Study design for triple negative breast cancer (TNBC) PDX

Group No.	Drug	No. Animals	Dose (mg/kg)	Volume (mL/kg)	Route	Regimen	Duration
1	Vehicle	6	0	10	PO	QD	21
3	Compound 1	6	30	10	PO	QD	21
5	Capivasertib	6	100	10	PO	BIDx3, QDx19	21

Table 11. Study design for TNBC PDX

Group No.	Drug	Dose (mg/kg)	AUClast (h*ng/mL)
1	Vehicle	0	0
2	Compound 1	30	46578
5	Capivasertib	100	Not measured

Example 8: Evaluation of the Antitumor Activity of Compound 1 in Human HR+ HER2-low Breast Cancer Xenograft Mouse Models

[00252] For human AKT1 E17K-mutated HR+ HER2-low breast cancer patient-derived xenograft (PDX) mouse models, Compound 1 and Ribociclib were administered either in

combination (e.g., Compound 1 and Ribociclib) or as a monotherapy (e.g., Compound 1 or Ribociclib). Treatments started when the mean tumor volume reached approximately 175 mm^3, as indicated in **Figure 4A**. Animals were monitored for tumor growth, body weight changes, and general health/behavior. Mice were assigned to respective groups based on their starting tumor volume and body weight such that the average values were the same for each treatment group. The study design indicating the groups (*e.g.*, drug treatment) and number of animals per group are shown below in **Table 12** and **Table 13 (**includes plasma drug concentration (AUC_{last})).

[00253] Briefly, Compound 1 and/or Ribociclib were dosed orally (PO) once per day (QD) in mice bearing patient derived breast cancer (HR+ HER2-low) tumor fragments. Compound 1 and Ribociclib were well-tolerated in mouse xenograft models of human HR+ HER2-low breast cancer (see **Figure 4B**). Compound 1 monotherapy induced tumor growth inhibition (TGI) of 19% at 4 mg/kg QD, 88% at 8 mg/kg QD, and 107% at 30 mg/kg QD (depicted in **Figure 4A**). Ribociclib monotherapy induced a TGI of 12% at 75 mg/kg QD. Compound 1 (concentrations of 2 mg/kg QD, 4 mg/kg QD, and 8 mg/kg QD) dosed in combination with Ribociclib (75 mg/kg QD) induced tumor growth inhibition (TGI) of 69%, 97%, and 106%, respectively (see **Figure 4A**). As shown in **Figure 4C**, no adverse hyperglycemia was observed with Compound 1 monotherapy, with mean blood glucose values (one hour post final dose) of 175 mg/dL at 2 mg/kg QD, 210 mg/dL at 4 mg/kg QD, 190 mg/dL at 8 mg/kg QD, and 176 mg/dL at 30 mg/kg QD. In addition, no adverse hyperglycemia was observed with Compound 1 in combination with 75 mg/kg QD of Ribociclib (see **Figure 4C**), with mean blood glucose values (one hour post final dose) of 198 mg/dL at 2 mg/kg QD, 182 mg/dL at 4 mg/kg QD, and 204 mg/dL at 8 mg/kg QD. For Ribociclib monotherapy, mean blood glucose values of 185 mg/dL at 75 mg/kg QD were observed. Mean blood glucose values of 176 mg/dL for the vehicle were observed.

Table 12. Study design for HR+ HER2-low breast cancer PDX

Group No.	Drug	No. Animals	Dose (mg/kg)	Volume (mL/kg)	Route	Regimen	Duration
1	Vehicle	6	0	10	PO	QD	56
2	Compound 1	8	2	10	PO	QD	56
3	Compound 1	8	4	10	PO	QD	56
4	Compound 1	8	8	10	PO	QD	56
5	Compound 1	6	30	10	PO	QD	56
6	Ribociclib	8	75	10	PO	QD	56

Group No.	Drug	No. Animals	Dose (mg/kg)	Volume (mL/kg)	Route	Regimen	Duration
7	Compound 1	8	2	10	PO	QD	56
	Ribociclib		75	10	PO	QD	
8	Compound 1	8	4	10	PO	QD	56
	Ribociclib		75	10	PO	QD	
9	Compound 1	8	8	10	PO	QD	56
	Ribociclib		75	10	PO	QD	

*Some animals from Groups 1, 2, 3 and 6 were sacrificed earlier due to the maximum tumor burden reached.

Table 13. Study design for HR+ HER2-low breast cancer PDX

Group No.	Drug	Dose (mg/kg)	AUClast (h*ng/mL)
1	Vehicle	0	0
2	Compound 1	2	1361
3	Compound 1	4	3789
4	Compound 1	8	9331
5	Compound 1	30	20066
6	Ribociclib	75	43937
7	Compound 1	2	2935
	Ribociclib	75	45758
8	Compound 1	4	5183
	Ribociclib	75	50742
9	Compound 1	8	13098
	Ribociclib	75	55166

[00254] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure.

CLAIMS

We claim:

1. A method of treating a cancer in a patient in need thereof, comprising administering to the patient 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.
2. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.
3. The method of claim 1 or 2, wherein the cancer is breast cancer.
4. The method of claim 3, wherein the cancer is a hormone receptor positive (HR+) breast cancer.
5. The method of claim 3, wherein the cancer is a human epidermal growth factor receptor 2 negative (HER2-) breast cancer.
6. The method of claim 3, wherein the cancer is a HR+/HER2- breast cancer.
7. The method of claim 3, wherein the cancer is a HR+/HER2-low breast cancer.
8. The method of claim 3, wherein the cancer is a HR+/HER2+ breast cancer.
9. The method of claim 3, wherein the cancer is a triple negative breast cancer (TNBC).
10. The method of claim 3, wherein the cancer is an invasive breast cancer.
11. The method of claim 1 or 2, wherein the cancer is uterine cancer.
12. The method of claim 11, wherein the cancer is uterine sarcoma.
13. The method of claim 11, wherein the cancer is endometrial cancer.
14. The method of claim 11, wherein the cancer is Type I endometrial cancer.
15. The method of claim 11, wherein the cancer is Type II endometrial cancer.
16. The method of claim 15, wherein the cancer is Type II endometrial papillary serous carcinoma.
17. The method of claim 15, wherein the cancer is Type II endometrial clear cell carcinoma.
18. The method of claim 15, wherein the cancer is Type II endometrial undifferentiated carcinoma.
19. The method of claim 15, wherein the cancer is Type II endometrioid carcinoma.

20. The method of claim 11, wherein the cancer is microsatellite instability (MSI) high and/or DNA mismatch repair (MMR) deficient.
21. The method of claim 11, wherein the cancer is tumor mutational burden (TMB) high.
22. The method of claim 11, wherein the cancer is HER2-.
23. The method of claim 1 or 2, wherein the cancer is cervical cancer.
24. The method of claim 23, wherein the cancer is a cervical squamous cell carcinoma.
25. The method of claim 23, wherein the cancer is a cervical adenocarcinoma.
26. The method of claim 1 or 2, wherein the cancer is prostate cancer.
27. The method of claim 26, wherein the cancer is prostate adenocarcinoma.
28. The method of claim 26, wherein the cancer is prostate neuroendocrine cancer.
29. The method of claim 26, wherein the cancer is prostate small cell neuroendocrine cancer.
30. The method of claim 26, wherein the cancer is prostate large cell carcinoma.
31. The method of claim 26, wherein the cancer is prostate transitional cell carcinoma.
32. The method of claim 26, wherein the cancer is prostate sarcoma.
33. The method of claim 1 or 2, wherein the cancer is bladder cancer.
34. The method of claim 33, wherein the cancer is urothelial cancer.
35. The method of claim 33, wherein the cancer is squamous cell cancer of the bladder.
36. The method of claim 33, wherein the cancer is small cell cancer of the bladder.
37. The method of claim 33, wherein the cancer is adenocarcinoma of the bladder.
38. The method of claim 1 or 2, wherein the cancer is lung cancer.
39. The method of claim 1 or 2, wherein the cancer is non-small cell lung cancer.
40. The method of claim 1 or 2, wherein the cancer is non-squamous non-small cell lung cancer.
41. The method of claim 1 or 2, wherein the cancer is squamous non-small cell lung cancer.
42. The method of claim 1 or 2, wherein the cancer is colon cancer.
43. The method of claim 1 or 2, wherein the cancer is anal cancer.
44. The method of claim 1 or 2, wherein the cancer is a meningioma.
45. The method of claim 1 or 2, wherein the cancer is a glioma.
46. The method of claim 1 or 2, wherein the cancer is pancreatic cancer.
47. The method of claim 46, wherein the cancer is exocrine pancreatic cancer.
48. The method of claim 46, wherein the cancer is neuroendocrine pancreatic cancer.
49. The method of claim 1 or 2, wherein the cancer is thyroid cancer.

50. The method of claim 1 or 2, wherein the cancer is sarcoma.
51. The method of claim 50, wherein the cancer is soft tissue sarcoma.
52. The method of claim 50, wherein the cancer is liposarcoma.
53. The method of claim 50, wherein the cancer is angiosarcoma.
54. The method of claim 50, wherein the cancer is osteosarcoma.
55. The method of claim 50, wherein the cancer is leiomyosarcoma.
56. The method of claim 50, wherein the cancer is rhabdomyosarcoma.
57. The method of claim 50, wherein the cancer is myxofibrosarcoma.
58. The method of claim 1 or 2, wherein the cancer is parotid gland cancer.
59. The method of claim 1 or 2, wherein the cancer is esophageal cancer.
60. The method of claim 1 or 2, wherein the cancer is stomach cancer.
61. The method of claim 1 or 2, wherein the cancer is skin cancer.
62. The method of claim 61, wherein the cancer is nonmelanoma skin cancer.
63. The method of claim 61, wherein the cancer is squamous nonmelanoma skin cancer.
64. The method of claim 61, wherein the cancer is non-squamous nonmelanoma skin cancer.
65. The method of claim 1 or 2, wherein the cancer is ovarian cancer.
66. The method of claim 65, wherein the cancer is epithelial ovarian cancer.
67. The method of claim 65, wherein the cancer is serous epithelial ovarian cancer.
68. The method of claim 65, wherein the cancer is endometrioid ovarian cancer.
69. The method of claim 65, wherein the cancer is clear cell ovarian cancer.
70. The method of claim 65, wherein the cancer is mucinous ovarian cancer.
71. The method of claim 1 or 2, wherein the cancer is adenoid cystic carcinoma.
72. The method of claim 1 or 2, wherein the cancer is renal cell cancer.
73. The method of claim 1 or 2, wherein the cancer is appendix cancer.
74. The method of claim 1 or 2, wherein the cancer is multiple myeloma.
75. The method of claim 1 or 2, wherein the cancer is acute myeloid leukemia.
76. The method of claim 1 or 2, wherein the cancer is cancer of unknown primary.
77. The method of claim 1 or 2, wherein the cancer is locally advanced.
78. The method of any one of the preceding claims, wherein the cancer is metastatic.
79. The method of any one of the preceding claims, wherein the method is adjuvant therapy following surgical resection.
80. The method of any one of the preceding claims, wherein the method is neo-adjuvant therapy.

81. The method of any one of the preceding claims, wherein the method is first-line systemic therapy for locally advanced or metastatic disease.
82. The method of any one of the preceding claims, wherein the patient has relapsed after prior therapy.
83. The method of any one of the preceding claims, wherein the patient has acquired resistance to prior therapy.
84. The method of any one of the preceding claims, wherein the patient is refractory to therapy.
85. The method of any one of claims 3-10, wherein the patient has shown progression on at least one CDK4/6 inhibitor.
86. The method of any one of claims 3-10, wherein the patient has shown progression on at least one endocrine-based regimen.
87. The method of any one of the preceding claims, wherein the patient has shown progression on cytotoxic chemotherapy.
88. The method of any one of the preceding claims, wherein the cancer is characterized by existence of AKT1-E17K mutation.
89. The method of any one of the preceding claims, wherein the cancer exhibits one or more co-occurring alterations selected from a PIK3CA alteration, a PIK3R1 alteration, an AKT1 alteration, and PTEN alteration.
90. The method of any one of the preceding claims, wherein the patient exhibits risk factors for hyperglycemia.
91. The method of any one of the preceding claims, wherein the patient exhibits risk factors selected from obesity, body mass index greater than or equal to 30, fasting blood glucose over 160 mg/dL, HbA1c greater than 6.0.
92. The method of any one of the preceding claims, wherein the patient exhibits Type I diabetes, diabetes requiring insulin, diabetes requiring metformin or another oral hypoglycemic agent, or pre-diabetes treated with metformin or another oral hypoglycemic agent.
93. A method of treating a cancer in a patient in need thereof, comprising administering to the patient:

(a) a composition comprising 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof; and

(b) at least one oncology therapeutic selected from an endocrine therapy, a hormonal therapy, an aromatase inhibitor, a selective estrogen receptor modulator (SERM) therapy, a selective estrogen receptor degrader (SERD) therapy, an anti-androgen, an androgen deprivation therapy, a taxane, a platinum agent, an anthracycline, an anti-metabolite, an alkylating agent, a microtubule affecting agent, an immune checkpoint inhibitor, a kinase inhibitor, a phosphatidylinositol 3-kinase (PI3K) inhibitor, a human epidermal growth factor receptor 2 (HER2) inhibitor, an antibody, a poly-ADP ribose polymerase (PARP) inhibitor, an antibody drug conjugate (ADC), a radiopharmaceutical, a neurotrophic tyrosine receptor kinase (NTRK) inhibitor, a rearranged during transfection (RET) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a mammalian target of rapamycin (mTOR) inhibitor, a rapidly accelerated fibrosarcoma (RAF) inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, or a cyclin dependent kinase (CDK) inhibitor.

94. The method of claim 93, wherein at least one oncology therapeutic is selected from an endocrine therapy, a hormonal therapy, a SERM therapy, a SERD therapy, an aromatase inhibitor, or an androgen deprivation therapy.
95. The method of claim 94, wherein the endocrine therapy, a hormonal therapy, a SERM therapy, a SERD therapy, an aromatase inhibitor, or an androgen deprivation therapy is selected from megestrol, exemestane, anastrozole, letrozole, tamoxifen, torimifene, raloxifene, fulvestrant, camizestrant, elacestrant, amcenestrant, giredestrant, imlunestrant, rintodestrant, SHR9549, ZN-c5, D0502, vepdegrestrant, palazestrant, AC682, DT2216, apalutamide, bicalutamide, darolutamide, enzalutamide, flutamide, nilutamide, abiraterone, buserelin, goserelin, leuprorelin, triptorelin, degarelix, or relugolix,.
96. The method of claim 93, wherein at least one oncology therapeutic is a taxane.
97. The method of claim 96, wherein the taxane is selected from paclitaxel, docetaxel, cabazitaxel, or abraxane.
98. The method of claim 93, wherein at least one oncology therapeutic is a platinum agent.
99. The method of claim 98, wherein the platinum agent is selected from cisplatin, carboplatin, or oxaliplatin.
100. The method of claim 93, wherein at least one oncology therapeutic is an anthracycline.
101. The method of claim 100, wherein the anthracycline is selected from doxorubicin or epirubicin.

102. The method of claim 93, wherein at least one oncology therapeutic is an anti-metabolite.

103. The method of claim 102, wherein the anti-metabolite is selected from methotrexate, fluorouracil, pemetrexed, irinotecan, topotecan, capecitabine or gemcitabine.

104. The method of claim 93, wherein at least one oncology therapeutic is an alkylating agent.

105. The method of claim 104, wherein the alkylating agent is selected from ifosfamide, trabectedin, cyclophosphamide, melphalan, or dacarbazine.

106. The method of claim 93, wherein at least one oncology therapeutic is a microtubule affecting agent.

107. The method of claim 106, wherein the microtubule affecting agent is selected from ixabepilone, viborelbine, or eribulin.

108. The method of claim 93, wherein at least one oncology therapeutic is an immune checkpoint inhibitor.

109. The method of claim 108, wherein the immune checkpoint inhibitor is selected from a CTLA-4 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, or a bi-specific PD-1/CTLA4 inhibitor.

110. The method of claim 109, wherein the CTLA-4 inhibitor is selected from ipilimumab or tremelimumab.

111. The method of claim 109, wherein the PD-1 inhibitor is selected from spartalizumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab, dostarlimab, retifanlimab, or toripalimab.

112. The method of claim 111, wherein the bi-specific PD-1/CTLA4 inhibitor is selected from AK104, MGD019, XmAb20717, or MEDI5752.

113. The method of claim 93, wherein at least one oncology therapeutic is a kinase inhibitor.

114. The method of claim 113, wherein the kinase inhibitor is selected from lenvatinib, pazopanib, imatinib, sorafenib, or avutometinib.

115. The method of claim 93, wherein at least one oncology therapeutic is a PI3K inhibitor.

116. The method of claim 115, wherein the PI3K inhibitor is selected from copanlisib, alpelisib, idelalisib, duvelisib, umbralisib, or STX-478.

117. The method of claim 93, wherein at least one oncology therapeutic is a HER2 inhibitor.

118. The method of claim 117, wherein the HER2 inhibitor is selected from lapatinib, neratinib, tucatinib, pyrotinib, or afatinib.
119. The method of claim 93, wherein at least one oncology therapeutic is an antibody.
120. The method of claim 119, wherein the antibody is selected from trastuzumab, pertuzumab, margetuxumab, bevacizumab, or rituximab.
121. The method of claim 93, wherein at least one oncology therapeutic is a PARP inhibitor.
122. The method of claim 121, wherein the PARP inhibitor is selected from olaparib, rucaparib, talazoparib, or niraparib.
123. The method of claim 93, wherein at least one oncology therapeutic is an ADC.
124. The method of claim 123, wherein the antibody drug conjugate is selected from ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, sacituzumab govitecan, disitamab vedotin, tisotumab vedotin, raludotatug deruxtecan, ARX-788, datopotamab deruxtecan, patritumab deruxtecan, ladiratuzumab vedotin, HS-20089, pertuzumab, or margetuximab.
125. The method of claim 93, wherein at least one oncology therapeutic is a radiopharmaceutical.
126. The method of claim 125, wherein the radiopharmaceutical is [111In]/[89Zr]-trastuzumab.
127. The method of claim 93, wherein at least one oncology therapeutic is a NTRK inhibitor.
128. The method of claim 127, wherein the NTRK inhibitor is selected from entrectinib or larotrectinib.
129. The method of claim 93, wherein at least one oncology therapeutic is a RET inhibitor.
130. The method of claim 129, wherein the RET inhibitor is selpercatinib or pralsetinib.
131. The method of claim 93, wherein at least one oncology therapeutic is an EGFR inhibitor.
132. The method of claim 131, wherein the EGFR inhibitor is erlotinib, osimertinib, neratinib, cetuximab, gefitinib, panitumumab, dacomitinib, afatinib, lapatinib, necitumumab, mobocertinib, or vandetanib.
133. The method of claim 93, wherein at least one oncology therapeutic is a mTOR inhibitor.

134. The method of claim 133, wherein the mTOR inhibitor is deforolimus, everolimus, sirolimus, or temsirolimus.

135. The method of claim 93, wherein at least one oncology therapeutic is a RAF inhibitor.

136. The method of claim 135, wherein the RAF inhibitor is vemurafenib, dabrafenib, encorafenib, tovorafenib, naporafenib, belvarafenib, or exarafenib.

137. The method of claim 93, wherein at least one oncology therapeutic is a MEK inhibitor.

138. The method of claim 137, wherein the MEK inhibitor is binimetinib, cobimetinib, trametinib, selumetinib, pimasertib, avutometinib, IMM-1-104, or NST-628.

139. The method of claim 93, wherein at least one oncology therapeutic is a CDK inhibitor.

140. The method of claim 139, wherein the CDK inhibitor is selected from palbociclib, abemaciclib, ribociclib, tagtociclib, ebvaciclib, lerociclib, PF-07220060, BLU-222, INX-315, or AVZO-021.

141. A method of treating a cancer in a patient in need thereof, comprising administering to the patient:

(a) a composition comprising 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof; and

(b) at least one oncology therapeutic selected from CAR-T therapy, tumor-infiltrating lymphocytes (TIL) or a neoantigen vaccine.

142. The method of any one of claims 93-141, wherein the cancer is breast cancer.

143. The method of claim 142, wherein the cancer is a hormone receptor positive (HR+) breast cancer.

144. The method of claim 142, wherein the cancer is a human epidermal growth factor receptor 2 negative (HER2-) breast cancer.

145. The method of claim 142, wherein the cancer is a HR+/HER2- breast cancer.

146. The method of claim 142, wherein the cancer is a HR+/HER2-low breast cancer.

147. The method of claim 142, wherein the cancer is a HR+/HER2+ breast cancer.

148. The method of claim 142, wherein the cancer is a triple negative breast cancer (TNBC).

149. The method of claim 142, wherein the cancer is an invasive breast cancer.

150. The method of any one of claims 93-141, wherein the cancer is uterine cancer.

151. The method of claim 150, wherein the cancer is uterine sarcoma.
152. The method of claim 150, wherein the cancer is endometrial cancer.
153. The method of claim 150, wherein the cancer is Type I endometrial cancer.
154. The method of claim 150, wherein the cancer is Type II endometrial cancer.
155. The method of claim 154, wherein the cancer is Type II endometrial papillary serous carcinoma.
156. The method of claim 154, wherein the cancer is Type II endometrial clear cell carcinoma.
157. The method of claim 154, wherein the cancer is Type II endometrial undifferentiated carcinoma.
158. The method of claim 154, wherein the cancer is Type II endometrioid carcinoma.
159. The method of claim 150, wherein the cancer is microsatellite instability (MSI) high and/or DNA mismatch repair (MMR) deficient.
160. The method of claim 150, wherein the cancer is tumor mutational burden (TMB) high.
161. The method of claim 150, wherein the cancer is HER2-.
162. The method of any one of claims 93-141, wherein the cancer is cervical cancer.
163. The method of claim 162, wherein the cancer is a cervical squamous cell carcinoma.
164. The method of claim 162, wherein the cancer is a cervical adenocarcinoma.
165. The method of any one of claims 93-141, wherein the cancer is prostate cancer.
166. The method of claim 165, wherein the cancer is prostate adenocarcinoma.
167. The method of claim 165, wherein the cancer is prostate neuroendocrine cancer.
168. The method of claim 165, wherein the cancer is prostate small cell neuroendocrine cancer.
169. The method of claim 165, wherein the cancer is prostate large cell carcinoma.
170. The method of claim 165, wherein the cancer is prostate transitional cell carcinoma.
171. The method of claim 165, wherein the cancer is prostate sarcoma.
172. The method of any one of claims 93-141, wherein the cancer is bladder cancer.
173. The method of claim 172, wherein the cancer is urothelial cancer.
174. The method of claim 172, wherein the cancer is squamous cell cancer of the bladder.
175. The method of claim 172, wherein the cancer is small cell cancer of the bladder.
176. The method of claim 172, wherein the cancer is adenocarcinoma of the bladder.
177. The method of any one of claims 93-141, wherein the cancer is lung cancer.

178. The method of any one of claims 93-141, wherein the cancer is non-small cell lung cancer.
179. The method of any one of claims 93-141, wherein the cancer is non-squamous non-small cell lung cancer.
180. The method of any one of claims 93-141, wherein the cancer is squamous non-small cell lung cancer.
181. The method of any one of claims 93-141, wherein the cancer is colon cancer.
182. The method of any one of claims 93-141, wherein the cancer is anal cancer.
183. The method of any one of claims 93-141, wherein the cancer is a meningioma.
184. The method of any one of claims 93-141, wherein the cancer is a glioma.
185. The method of any one of claims 93-141, wherein the cancer is pancreatic cancer.
186. The method of claim 185, wherein the cancer is exocrine pancreatic cancer.
187. The method of claim 185, wherein the cancer is neuroendocrine pancreatic cancer.
188. The method of any one of claims 93-141, wherein the cancer is thyroid cancer.
189. The method of any one of claims 93-141, wherein the cancer is sarcoma.
190. The method of claim 189, wherein the cancer is soft tissue sarcoma.
191. The method of claim 189, wherein the cancer is liposarcoma.
192. The method of claim 189, wherein the cancer is angiosarcoma.
193. The method of claim 189, wherein the cancer is osteosarcoma.
194. The method of claim 189, wherein the cancer is leiomyosarcoma.
195. The method of claim 189, wherein the cancer is rhabdomyosarcoma.
196. The method of claim 189, wherein the cancer is myxofibrosarcoma.
197. The method of any one of claims 93-141, wherein the cancer is parotid gland cancer.
198. The method of any one of claims 93-141, wherein the cancer is esophageal cancer.
199. The method of any one of claims 93-141, wherein the cancer is stomach cancer.
200. The method of any one of claims 93-141, wherein the cancer is skin cancer.
201. The method of claim 200, wherein the cancer is nonmelanoma skin cancer.
202. The method of claim 201, wherein the cancer is squamous nonmelanoma skin cancer.
203. The method of claim 201, wherein the cancer is non-squamous nonmelanoma skin cancer.
204. The method of any one of claims 93-141, wherein the cancer is ovarian cancer.
205. The method of claim 204, wherein the cancer is epithelial ovarian cancer.
206. The method of claim 204, wherein the cancer is serous epithelial ovarian cancer.

207. The method of claim 204, wherein the cancer is endometrioid ovarian cancer.
208. The method of claim 204, wherein the cancer is clear cell ovarian cancer.
209. The method of claim 204, wherein the cancer is mucinous ovarian cancer.
210. The method of any one of claims 93-141, wherein the cancer is adenoid cystic carcinoma.
211. The method of any one of claims 93-141, wherein the cancer is renal cell cancer.
212. The method of any one of claims 93-141, wherein the cancer is appendix cancer.
213. The method of any one of claims 93-141, wherein the cancer is multiple myeloma.
214. The method of any one of claims 93-141, wherein the cancer is acute myeloid leukemia.
215. The method of any one of claims 93-141, wherein the cancer is cancer of unknown primary.
216. The method of any one of claims 93-141, wherein the cancer is locally advanced.
217. The method of any one of the preceding claims, wherein the cancer is metastatic.
218. The method of any one of the preceding claims, wherein the method is adjuvant therapy following surgical resection.
219. The method of any one of the preceding claims, wherein the method is neo-adjuvant therapy.
220. The method of any one of the preceding claims, wherein the method is first-line systemic therapy for locally advanced or metastatic disease.
221. The method of any one of the preceding claims, wherein the patient has relapsed after prior therapy.
222. The method of any one of the preceding claims, wherein the patient has acquired resistance to prior therapy.
223. The method of any one of the preceding claims, wherein the patient is refractory to therapy.
224. The method of any one of claims 142-149, wherein the patient has shown progression on at least one CDK4/6 inhibitor.
225. The method of any one of claims 142-149, wherein the patient has shown progression on at least one endocrine-based regimen.
226. The method of any one of the preceding claims, wherein the patient has shown progression on cytotoxic chemotherapy.
227. The method of any one of the preceding claims, wherein the cancer is characterized by existence of AKT1-E17K mutation.

228. The method of any one of claims 93-227, wherein the cancer exhibits one or more co-occurring alterations selected from a PIK3CA alteration, a PIK3R1 alteration, an AKT1 alteration, and PTEN alteration.

229. The method of any one of the preceding claims, wherein the patient exhibits risk factors for hyperglycemia.

230. The method of any one of the preceding claims, wherein the patient exhibits risk factors selected from obesity, body mass index greater than or equal to 30, fasting blood glucose over 160 mg/dL, HbA1c greater than 6.0.

231. The method of any one of the preceding claims, wherein the patient exhibits Type I diabetes, diabetes requiring insulin, diabetes requiring metformin or another oral hypoglycemic agent, or pre-diabetes treated with metformin or another oral hypoglycemic agent.

232. The method of any one of the preceding claims, wherein the 4-((1-(4-(2-(2-aminopyridin-3-yl)-5-(5-fluoropyridin-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)piperidin-4-yl)amino)pyrimidine-2-carbonitrile, or pharmaceutically acceptable salt or solvate thereof, is administered orally.

233. The method of any one of the preceding claims, wherein the oral administration occurs once per day, twice per day, three times per day, every other day, or one to six days per week.