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(71) **Applicant**: **SPEROVIE BIOSCIENCES, INC.** [US/US]; 113 Cedar Street, Milford, Massachusetts 01757 (US).

(72) **Inventors**: **IYER, Radhakrishnan, P.**; 15 Quail Hollow Drive, Shrewsbury, MA 01545 (US). **SHERI, Anjaneyulu**; 12 Pheasant Hill Drive, Shrewsbury, MA 01545 (US). **PADMANABHAN, Seetharamaiyer**; 67 Fottler Avenue, Lexington, MA 02420 (US). **GIMI, Rayormand, H.**; 41 Stonrgate Road, Chelmosford, MA 01824 (US). **CLEARY, Dillon**; 99 Spruce Street, Middleborough, MA 02346 (US). **KHEDKAR, Santosh**; 28 Homestead St., Lexington, MA 02421 (US). **CHALLA, Sreerupa**; 3132 Arbor Dr., Shrewsbury, MA 01545 (US).

(74) **Agent**: **GORDON, Dana, M.**; Foley Hoag LLP, Seaport West, 155 Seaport Boulevard, Boston, MA 02210-2600 (US).

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(54) **Title**: COMPOUNDS AND COMPOSITIONS FOR THE TREATMENT OF DISEASE

(57) **Abstract**: This invention relates to compounds (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) and compositions for use in modulating PDE4 as well as the preventing and treating a PDE4-mediated disease in a subject.

COMPOUNDS AND COMPOSITIONS FOR THE TREATMENT OF DISEASE

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 62/277,930, filed January 12, 2016, and U.S. Application No. 62/277,931, filed January 12, 2016, the disclosure of each of which is incorporated herein by reference in its entirety.

FIELD OF INVENTION

This invention relates to compounds and compositions for use in inhibition of PDE4 as well as the prevention and treatment of a PDE4-mediated disease in a subject, in particular a neurodegenerative disease or an inflammatory disease.

BACKGROUND OF INVENTION

Cyclic dinucleotide phosphodiesterases (PDEs) are a class of enzymes responsible for the hydrolysis and resulting inactivation of cyclic dinucleotide second messengers, particularly cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP). These enzymes are largely distributed throughout the mammalian central nervous system and immune system, and play a critical role in regulating intracellular signaling cascades by controlling second messenger concentration. Early studies of PDE enzymes date to the 1950s, in a series of publications by Sutherland and Rall outlining the properties of cAMP (Sutherland, E.W. and Rall, T. *J Am Chem Soc* (1957) 79:3608; Rall, T and Sutherland, E. W. *J Biol Chem* (1958) 232:1077-1091). To date, eleven different PDE families have been described, each family comprising multiple isoforms and splice variants. Classification of PDEs is largely based on sequence homogeneity, substrate specificity, tissue and intracellular distribution, and other biochemical properties.

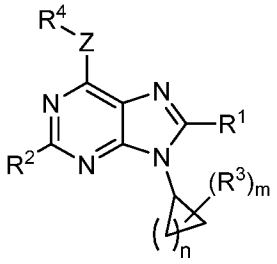
PDE4 is widely expressed in various tissues including the central nervous system and is encoded by four genes (PDE4A-PDE4D) that result in over 20 different variants of the enzyme. The common feature of all PDE4 isoforms is the ability to hydrolyze cAMP through a conserved catalytic domain comprising a tripartite structure (Houslay, M.D. et al. *Circ Res* (2007) 100:950-966). Although the specific function of each PDE4 isoform within the larger context of cellular

homeostasis is still unclear, the activity of each isoform has been shown to be regulated by a number of kinases and phosphatases, suggesting that each carries out an important role in various aspects of controlling intracellular cAMP concentration. Due to the far-reaching effects of PDE4 enzymes, development of PDE4 inhibitors is currently an active area of research in relation to treatment and prevention of a number of diseases, particularly neurodegenerative and inflammatory diseases. To date, roflumilast has been approved by the FDA as a PDE4 inhibitor for the treatment of COPD and apremilast has been approved as a PDE4 inhibitor for the treatment of psoriasis, although several others are currently in different phases of clinical trials. Despite this progress, the high prevalence of side effects such as emesis and the lack of specific PDE4 isoforms have hampered the development of successful therapies. As such, there is a need for a new generation of PDE4 inhibitors with improved clinical efficacy, lowered toxicity, and an overall better safety profile.

SUMMARY OF THE INVENTION

Described herein are compounds and compositions useful for modulating the family of PDE4 enzymes. The present invention further provides methods of preventing and treating a PDE4-mediated disease in a subject, e.g., neurodegenerative disease or an inflammatory disease.

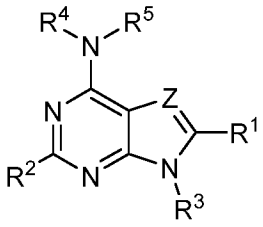
In one aspect, the present invention features a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein Z, R^1, R^2, R^3, R^4, m, n, and subvariables thereof are as described herein.

In another aspect, the present invention features a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein Z, R^1, R^2, R^3, R^4, R^5, and subvariables thereof are as described herein.

In another aspect, the present invention features a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable excipient or carrier. In some embodiments, a pharmaceutical composition described herein includes a therapeutically effective amount of a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof. The pharmaceutical composition may be useful for preventing or treating preventing a neurodegenerative disease or an inflammatory disease.

In another aspect, the present invention features a method for inhibiting PDE4 activity in a cell or in a subject (e.g., PDE4B1 activity), comprising contacting the cell or administering to a subject an effective amount of a compound or a pharmaceutical composition described herein (e.g., a composition comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof).

In another aspect, the present invention features method for the treatment of a neurodegenerative disease or disorder comprising administering to a subject an effective amount of a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition thereof. In some embodiments, the neurodegenerative disease or disorder comprises Alzheimer's disease, Huntington's disease, Parkinson's disease, dementia, amyotrophic lateral sclerosis, or motor neuron disease.

In another aspect, the present invention features a method for the treatment of an inflammatory disease or disorder comprising administering to a subject an effective amount of a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition thereof. In some embodiments, the inflammatory disease or disorder comprises COPD, an allergy, asthma, dermatitis, psoriasis, irritable bowel syndrome, or ulcerative colitis.

In another aspect, the present invention features a kit comprising a container with a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, a kits described herein further includes instructions for administering the compound of Formula (I) or Formula (II) or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof.

The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, Examples, and Claims.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure relates to compounds, compositions, and methods directed to the inhibition of a PDE4 isoform (e.g., PDE4B1). In addition, the disclosure relates to methods of treating a subject inflicted with a PDE4-mediated disorder, such as a neurodegenerative disease or an inflammatory disease.

Definitions

As used herein, the articles "a" and "an" refer to one or to more than one (*e.g.,* to at least one) of the grammatical object of the article.

"About" and "approximately" generally refer to an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

As used herein, the term “acquire” or “acquiring” as the terms are used herein, refer to obtaining possession of a physical entity (*e.g.*, a sample, *e.g.*, blood sample or liver biopsy specimen), or a value, *e.g.*, a numerical value, by “directly acquiring” or “indirectly acquiring” the physical entity or value. “Directly acquiring” means performing a process (*e.g.*, an analytical method) to obtain the physical entity or value. “Indirectly acquiring” refers to receiving the physical entity or value from another party or source (*e.g.*, a third party laboratory that directly acquired the physical entity or value). Directly acquiring a value includes performing a process that includes a physical change in a sample or another substance, *e.g.*, performing an analytical

process which includes a physical change in a substance, *e.g.*, a sample, performing an analytical method, *e.g.*, a method as described herein, *e.g.*, by sample analysis of bodily fluid, such as blood by, *e.g.*, mass spectroscopy (*e.g.* LC-MS), or PCR (*e.g.*, RT-PCR).

As used herein, an amount of a compound, conjugate, or substance effective to treat a disorder (*e.g.*, a disorder described herein), "therapeutically effective amount," "effective amount" or "effective course" refers to an amount of the compound, substance, or composition which is effective, upon single or multiple dose administration(s) to a subject, in treating a subject, or in curing, alleviating, relieving or improving a subject with a disorder (*e.g.*, a neurodegenerative or inflammatory disease mediated by PDE4) beyond that expected in the absence of such treatment.

As used herein, the terms "prevent" or "preventing" as used in the context of a disorder or disease, refer to administration of an agent to a subject, *e.g.*, the administration of a compound of the present invention (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof, e.g., as described herein) to a subject, such that the onset of at least one symptom of the disorder or disease is delayed as compared to what would be seen in the absence of administration of said agent.

As used herein, the term "subject" is intended to include human and non-human animals. Exemplary human subjects include a human patient having a disorder, *e.g.*, a disorder described herein (e.g., a neurodegenerative disease or an inflammatory disease), or a normal subject. The term "non-human animals" includes all vertebrates, *e.g.*, non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, *e.g.*, sheep, dogs, cats, cows, pigs, etc.

As used herein, the terms "treat" or "treating" a subject having a disorder or disease refer to subjecting the subject to a regimen, *e.g.*, the administration of a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof, such that at least one symptom of the disorder or disease is cured, healed, alleviated, relieved, altered, remedied, ameliorated, or improved. Treating includes administering an amount effective to alleviate, relieve, alter, remedy, ameliorate, improve or affect the disorder or disease, or the

symptoms of the disorder or disease. The treatment may inhibit deterioration or worsening of a symptom of a disorder or disease.

Numerous ranges, *e.g.,* ranges for the amount of a drug administered per day, are provided herein. In some embodiments, the range includes both endpoints. In other embodiments, the range excludes one or both endpoints. By way of example, the range can exclude the lower endpoint. Thus, in such an embodiment, a range of 100 to 1000 mg/day, excluding the lower endpoint, would cover an amount greater than 100 that is less than or equal to 1000 mg/day.

"Co-administration", "co-administering" or "co-providing", as used herein in the context of the administration of therapies, refers to administration at the same time, administration of one therapy before (*e.g.,* immediately before, less than about 5, about 10, about 15, about 30, about 45, about 60 minutes, about 1, about 2, about 3, about 4, about 6, about 8, about 10, about 12, about 16, about 20, about 24, about 48, about 72 or more hours before) administration of a secondary therapy.

"Course of therapy", as referred to herein, comprises one or more separate administrations of a therapeutic agent (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof). A course of therapy can comprise one or more cycles of a therapeutic agent.

A "cycle", as used herein in the context of a cycle of administration of a drug, refers to a period of time for which a drug is administered to a patient. For example, if a drug is administered for a cycle of 4 weeks days, the periodic administration, *e.g.,* daily or twice daily, is given for 4 weeks. A drug can be administered for more than one cycle. In some embodiments, the first and second or subsequent cycles are the same in terms of one or both of duration and periodic administration. In embodiments, a first and second or subsequent cycle differs in terms of one or both of duration and periodic administration. Rest periods may be interposed between cycles. A rest cycle may be about 1, about 2, about 4, about 6, about 8, about 10, about 12, about 16, about 20, or about 24 hours; or about 1, about 2, about 3, about 4, about 5, about 6, or about 7 days; or about 1, about 2, about 3, about 4 or more weeks in length.

Chemical Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl. For compounds of the invention in which a variable appears more than once, each variable can be a different moiety selected from the Markush group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties selected from the Markush group defined for R.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

As used herein, "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, and can have a number of carbon atoms as optionally designated (*i.e.*, C_1-C_6 refers to an alkyl chain comprising one to six carbons). Examples of saturated hydrocarbon groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, isopentyl, homologs and isomers of, for example, n-pentyl, n-hexyl, and the like.

As used herein, "alkenyl" can be a straight or branched hydrocarbon chain, containing at least one double bond, and having from two to six carbon atoms (*i.e.* C_2-C_6 alkenyl). Examples of alkenyl groups, include, but are not limited to, groups such as ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

As used herein, "alkoxy" is be a straight chain or branched alkyl group bound to an oxygen atom. Examples of alkoxy groups, include, but are not limited to, groups such as methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, tert-butyloxy, pentyloxy, or hexyloxy, and the like.

As used herein, "alkynyl" can be a straight or branched hydrocarbon chain, containing at least one triple bond, having from two to six carbon atoms (i.e. C_2-C_6 alkynyl). Examples of alkynyl groups, include, but are not limited to, groups such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

As used herein, "amine" and "amino" refer to the radical $-NH_2$. "Substituted amino" refers to an amino group of the formula $-N(R^{38})_2$ wherein R^{38} is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, or an amino protecting group, wherein at least one of R^{38} is not a hydrogen. In certain embodiments, each R^{38} is independently selected from hydrogen, C_1–C_8 alkyl, C_3–C_8 alkenyl, C_3–C_8 alkynyl, C_6–C_{10} aryl, 5–10 membered heteroaryl, 4–10 membered heterocyclyl, C_3–C_{10} cycloalkyl, $-(CH_2)_t(C_6$–C_{10} aryl), $-(CH_2)_t$(5–10 membered heteroaryl), $-(CH_2)_t(C_3$–C_{10} cycloalkyl), or $-(CH_2)_t$(4–10 membered heterocyclyl), wherein t is an integer between 0 and 8, or both R^{38} groups are joined to form an ring, e.g., a 3-8 membered ring (e.g., a 3-8 membered heterocyclyl or 3-8 membered heteroaryl ring).

As used herein, "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the

number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Aryl groups include, but are not limited to, phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

As used herein, "alkoxy" refers to -O-(alkyl), wherein the alkyl moiety is as defined herein.

As used herein, "arylalkyl" refers to an (aryl)alkyl— radical wherein aryl and alkyl moieties are as disclosed herein.

As used herein, "aryloxy" refers to -O-(aryl), wherein the aryl moiety is as defined herein.

As used herein, "carboxyl" refers to a –(C=O)OH radical.

As used herein, "cyano" refers to a –CN radical.

As used herein, the terms "cyclyl" and "cycloalkyl" refer to a monocyclic or polycyclic non-aromatic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (i.e. C_3-C_{10} cycloalkyl). Exemplary C_{3-6} cycloalkyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} cycloalkyl groups include, without limitation, the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} cycloalkyl groups include, without limitation, the aforementioned C_{3-8} cycloalkyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the cycloalkyl group is either monocyclic ("monocyclic cycloalkyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic cycloalkyl") and can be saturated or can be partially unsaturated. "Cycloalkyl" or "cyclyl" also includes ring systems wherein the cycloalkyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the cycloalkyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the cycloalkyl ring system.

As used herein, "ester" refers to a –(C=O)OR' radical, wherein R' is an alkyl, alkenyl, alkynyl, or heteroalkyl group.

As used herein, "halo" or "halogen," independently or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. The term "halide" by itself or as part of another substituent, refers to a fluoride, chloride, bromide, or iodide atom.

As used herein, "haloalkyl" and "haloalkoxy" refers to alkyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

As used herein, "heteroalkyl" refers to an alkyl that has one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given, e.g. C_1-C_6 heteroalkyl which refers to the number of carbons in the chain, which in this example includes 1 to 6 carbon atoms. For example, a $–CH_2OCH_2CH_3$ radical is referred to as a "C_3" heteroalkyl. Connection to the rest of the molecule may be through either a heteroatom or a carbon in the heteroalkyl chain.

As used herein, "heteroaryl" refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the

like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl,

benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

As used herein, the terms "heterocyclyl" and "heterocycloalkyl" refer to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, furanosyl, ribosyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin–2–one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl, and 5,6-dihydropyrimidinyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms

include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5–membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6–bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6–membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6–bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

As used herein, "hydroxy" or "hydroxyl" refers to a –OH radical.

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (*i.e.*, in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight,

more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

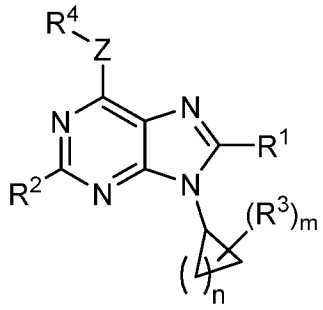
In the compositions provided herein, an enantiomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure R–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R–compound. In certain embodiments, the enantiomerically pure R–compound in such compositions can, for example, comprise, at least about 95% by weight R–compound and at most about 5% by weight S–compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure S–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S–compound. In certain embodiments, the enantiomerically pure S–compound in such compositions can, for example, comprise, at least about 95% by weight S–compound and at most about 5% by weight R–compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

Compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D or deuterium), and ^{3}H (T or tritium); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Compounds

The present invention features compounds and compositions for the inhibition of PDE4 and the treatment and prevention of PDE4-mediated disorders, such as a neurodegenerative disease or an inflammatory disease.

In one aspect, the present invention features a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein Z is O or NR^5; R^1 is H, C_1-C_6 alkyl, or C_1-C_6 heteroalkyl; R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, $C(O)R^A$, $C(O)OR^B$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^A$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, hydroxyl, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^6; R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, $C(O)R^A$, $C(O)OR^B$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^A$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, hydroxyl, oxo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7; R^4 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $C(O)OR^A$, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8; R^5 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8; or wherein R^4 and R^5 may be taken together to form a ring optionally substituted with 1-5 R^8; each of R^6 and R^7 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, oxo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^9; R^8 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, oxo, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9; each of R^A, R^B, R^C, R^D, and R^E is independently H, C_1-C_6 alkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9; or wherein R^C and R^D are taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl ring, optionally substituted with 1-5 R^9; R^9 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, hydroxyl, halo, oxo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted optionally substituted with 1-5 R^{10}; R^{10} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, halo, hydroxyl, or cycloalkyl; R^{11} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, halo, cyano, hydroxyl, or cycloalkyl; n is 1, 2, 3, 4, 5, 6; m is 0, 1, 2, 3, 4, 5, or 6; and p is 0, 1, or 2.

In some embodiments, R^1 is H or C_1-C_6 alkyl. In some embodiments, R^1 is H. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3).

In some embodiments, R^2 is C_1-C_6 alkyl, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, R^2 is NR^CR^D, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, R^2 is $S(O)_pR^E$, R^E is C_1-C_6 alkyl (e.g., CH_3), and p is 2.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$) or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is heterocyclyl, optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl, (e.g., a 5- or 6-membered nitrogen-containing heterocyclyl, e.g., pyrrolidinyl, piperidinyl, piperazinyl, e.g., pyrrolidinyl), each of which is optionally substituted with 1-5 R^6.

In some embodiments, R^2 is halo (e.g., chloro).

In some embodiments, R^2 is aryl (e.g., phenyl) or heteroaryl (e.g., pyridyl), each of which is optionally substituted with 1-5 R^6.

In some embodiments, R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7. In some embodiments, R^3 is hydroxyl or oxo. In some embodiments, R^3 is hydroxyl or oxo and n is 3 or 4. In some embodiments, R^3 is hydroxyl or oxo, n is 3 or 4, and m is 1.

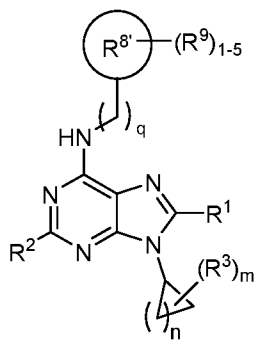
In some embodiments, Z is O. In some embodiments, Z is O and R^4 is C_1-C_6 alkyl (CH_2) or heterocyclyl (e.g., cyclopentyl), optionally substituted with 1-5 R^8.

In some embodiments, R^4 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^4 is H or C_1-C_6 alkyl (e.g., H or CH_3).

In some embodiments, Z is NR^5. In some embodiments, Z is NR^5 and R^5 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, or heteroaryl, wherein each alkyl, heteroalkyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8. In some embodiments, Z is NR^5 and R^5 is C_1-C_6 alkyl (e.g., -CH_2-), optionally substituted with 1-5 R^8. In some embodiments, Z is NR^5 and R^5 is C_1-C_6 alkyl (e.g., -CH_2-) substituted with 1 R^8. In some embodiments, R^8 is heterocyclyl or heteroaryl, wherein each heterocyclyl or heteroaryl is optionally substituted optionally substituted with 1-5 R^9. In some embodiments, R^8 is heteroaryl (e.g., monocyclic or bicyclic heteroaryl). In some embodiments, R^8 is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzofuranyl, benzoxazolyl, benzothiophenyl, indolyl, or benzoimidazolyl). In some embodiments, R^8 is benzothiazolyl.

In some embodiments, Z is NR^5 and R^4 and R^5 are taken together to form a heterocyclyl ring (e.g., a 5-membered heterocyclyl ring, e.g., pyrrolidinyl).

In some embodiments, the compound is a compound of Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein each R^1, R^2, R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, n, and p are defined as for Formula (I), $R^{8'}$ is heteroaryl, and q is 0, 1, 2, or 3.

In some embodiments, R^1 is H or C_1-C_6 alkyl. In some embodiments, R^1 is H. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3).

In some embodiments, R^2 is C_1-C_6 alkyl, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, R^2 is NR^CR^D, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, R^2 is $S(O)_pR^E$, R^E is C_1-C_6 alkyl (e.g., CH_3), and p is 2.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$) or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is heterocyclyl, optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl, (e.g., a 5- or 6-membered nitrogen-containing heterocyclyl, e.g., pyrrolidinyl, piperidinyl, piperazinyl, e.g., pyrrolidinyl), each of which is optionally substituted with 1-5 R^6.

In some embodiments, R^2 is halo (e.g., chloro).

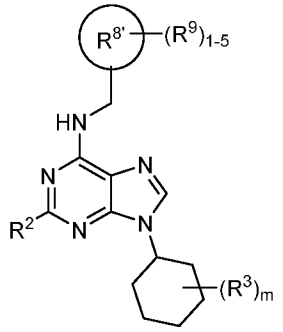
In some embodiments, R^2 is aryl (e.g., phenyl) or heteroaryl (e.g., pyridyl), each of which is optionally substituted with 1-5 R^6.

In some embodiments, R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7. In some embodiments, R^3 is hydroxyl or oxo. In some embodiments, R^3 is hydroxyl or oxo and m is 3 or 4. In some embodiments, R^4 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^4 is H or C_1-C_6 alkyl (e.g., H or CH_3).

In some embodiments, q is 1 or 2. In some embodiments, q is 1.

In some embodiments, $R^{8'}$ is heterocyclyl or heteroaryl, wherein each heterocyclyl or heteroaryl is optionally substituted optionally substituted with 1-5 R^9. In some embodiments, $R^{8'}$ is heteroaryl (e.g., monocyclic or bicyclic heteroaryl). In some embodiments, $R^{8'}$ is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzofuranyl, benzoxazolyl, benzothiophenyl, indolyl, or benzoimidazolyl). In some embodiments, $R^{8'}$ is benzothiazolyl.

In some embodiments, the compound is a compound of Formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein each R^2, R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I), and $R^{8'}$ is a nitrogen-containing bicyclic heteroaryl.

In some embodiments, R^2 is C_1-C_6 alkyl, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, R^2 is NR^CR^D, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, R^2 is $S(O)_pR^E$, R^E is C_1-C_6 alkyl (e.g., CH_3), and p is 2.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$) or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is heterocyclyl, optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl, (e.g., a 5- or 6-membered nitrogen-

containing heterocyclyl, e.g., pyrrolidinyl, piperidinyl, piperazinyl, e.g., pyrrolidinyl), each of which is optionally substituted with 1-5 R^6.

In some embodiments, R^2 is halo (e.g., chloro).

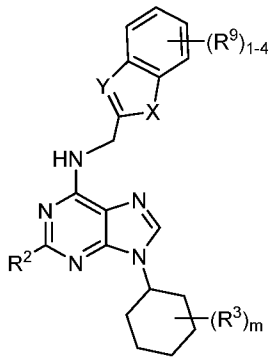
In some embodiments, R^2 is aryl (e.g., phenyl) or heteroaryl (e.g., pyridyl), each of which is optionally substituted with 1-5 R^6.

In some embodiments, R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7. In some embodiments, R^3 is hydroxyl or oxo. In some embodiments, R^3 is hydroxyl or oxo and m is 1.

In some embodiments, R^4 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^4 is H or C_1-C_6 alkyl (e.g., H or CH_3).

In some embodiments, $R^{8'}$ is heterocyclyl or heteroaryl, wherein each heterocyclyl or heteroaryl is optionally substituted optionally substituted with 1-5 R^9. In some embodiments, $R^{8'}$ is heteroaryl (e.g., monocyclic or bicyclic heteroaryl). In some embodiments, $R^{8'}$ is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzofuranyl, benzoxazolyl, benzothiophenyl, indolyl, or benzoimidazolyl). In some embodiments, $R^{8'}$ is benzothiazolyl.

In some embodiments, the compound is a compound of Formula (Ic):



(Ic)

or a pharmaceutically acceptable salt thereof, wherein each R^2, R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I), X is O, NH, CH_2, or S, and Y is N or CH.

In some embodiments, R^2 is C_1-C_6 alkyl, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl. In some embodiments, R^2 is NR^CR^D, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl,

aryl, or heteroaryl. In some embodiments, R^2 is $S(O)_pR^E$, R^E is C_1-C_6 alkyl (e.g., CH_3), and p is 2.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$) or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is heterocyclyl, optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl, (e.g., a 5- or 6-membered nitrogen-containing heterocyclyl, e.g., pyrrolidinyl, piperidinyl, piperazinyl, e.g., pyrrolidinyl), each of which is optionally substituted with 1-5 R^6.

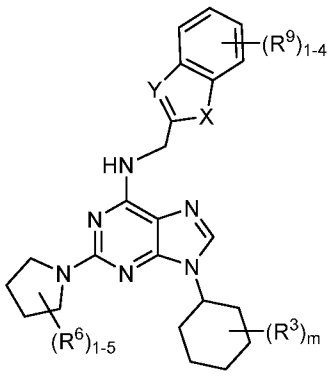
In some embodiments, R^2 is halo (e.g., chloro).

In some embodiments, R^2 is aryl (e.g., phenyl) or heteroaryl (e.g., pyridyl), each of which is optionally substituted with 1-5 R^6.

In some embodiments, R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7. In some embodiments, R^3 is hydroxyl or oxo. In some embodiments, R^3 is hydroxyl or oxo and m is 1.

In some embodiments, X is O. In some embodiments, X is NH. In some embodiments, X is CH_2. In some embodiments, X is S. In some embodiments, Y is N. In some embodiments, Y is CH. In some embodiments, X is S and Y is N.

In some embodiments, the compound is a compound of Formula (Id):



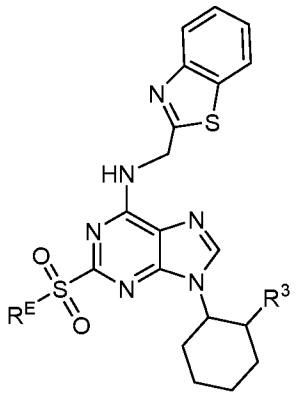
(Id)

or a pharmaceutically acceptable salt thereof, wherein each R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I), X is O, NH, CH_2, or S, and Y is N or CH.

In some embodiments, R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7. In some embodiments, R^3 is hydroxyl or oxo. In some embodiments, R^3 is hydroxyl or oxo and m is 1.

In some embodiments, X is O. In some embodiments, X is NH. In some embodiments, X is CH_2. In some embodiments, X is S. In some embodiments, Y is N. In some embodiments, Y is CH. In some embodiments, X is S and Y is N.

In some embodiments, the compound is a compound of Formula (Ie):

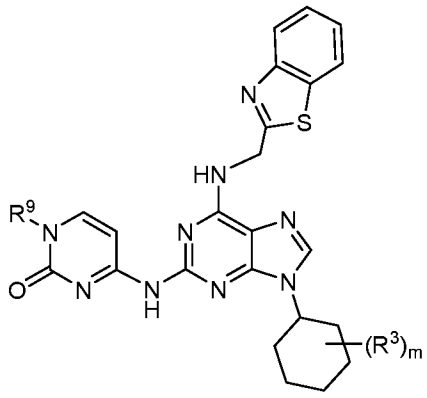


(Ie)

or a pharmaceutically acceptable salt thereof, wherein each R^3, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I).

In some embodiments, R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7. In some embodiments, R^3 is hydroxyl or oxo. In some embodiments, R^3 is hydroxyl or oxo and m is 1.

In some embodiments, the compound is a compound of Formula (If):



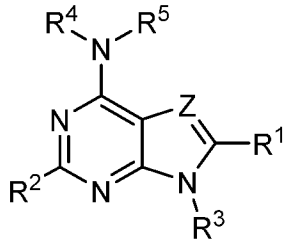
(If)

or a pharmaceutically acceptable salt thereof, wherein each R^3, R^7, R^9, R^{10}, and m are defined as for Formula (I).

In some embodiments, R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7. In some embodiments, R^3 is hydroxyl or oxo. In some embodiments, R^3 is hydroxyl or oxo and m is 1.

In some embodiments, R^9 is heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^9 is oxo. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In another aspect, the present invention features a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein Z is N or CH; R^1 is H, C_1-C_6 alkyl, or C_1-C_6 heteroalkyl; R^2 is C_1-C_6 heteroalkyl, $C(O)R^A$, $C(O)OR^B$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^A$, halo, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^6; R^3 is H, C_1-C_6 alkyl, or C_1-C_6 heteroalkyl optionally substituted with 1-5 R^7; R^4 is H, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally

substituted with 1-5 R^8; R^5 is H, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8; or wherein R^4 and R^5 may be taken together to form a ring optionally substituted with 1-5 R^8; each of R^6 and R^7 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cyano, oxo, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-6 R^9; R^8 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, oxo, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9; each of R^A, R^B, R^C, R^D, and R^E is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9; or wherein R^C and R^D are taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl ring, optionally substituted with 1-5 R^9; R^9 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, hydroxyl, halo, oxo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted optionally substituted with 1-5 R^{10}; R^{10} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, halo, hydroxyl, or cycloalkyl; R^{11} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, halo, cyano, hydroxyl, or cycloalkyl; and p is 0, 1, or 2.

In some embodiments, Z is N. In some embodiments, Z is CH.

In some embodiments, R^1 is H or C_1-C_6 alkyl. In some embodiments, R^1 is H. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3).

In some embodiments, R^2 is C_1-C_6 heteroalkyl, NR^CR^D, $NR^CC(O)R^B$, halo, cycloalkyl, or heterocyclyl. In some embodiments, R^2 is NR^CR^D. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl, heterocyclyl, aryl, or heteroaryl, optionally substituted with 1-5 R^9. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-

dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is heterocyclyl optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl (e.g., a 6-membered nitrogen-containing heterocyclyl, e.g., piperazinyl, piperidinyl, morphilinyl), each of which is optionally substituted with 1-5 R^6 (e.g., $C(O)R^B$, oxo). In some embodiments, R^6 is $C(O)R^B$ or oxo, and R^B is C_1-C_6 heteroalkyl (e.g., methoxy).

In some embodiments, R^2 is halo (e.g., chloro).

In some embodiments, R^3 is H, C_1-C_6 alkyl (e.g., CH_2), or C_1-C_6 heteroalkyl (e.g., $CH_2CH_2OCH_3$ or CH_2CH_2N-), substituted with 0-2 R^7 (e.g., -$(C(O)OCH_3)_2$). In some embodiments, R^3 is H. In some embodiments, R^3 is C_1-C_6 alkyl (e.g., CH_2) substituted with 1 R^7. In some embodiments, R^3 is C_1-C_6 heteroalkyl (e.g., $CH_2CH_2OCH_3$ or CH_2CH_2N-) substituted with 0-2 R^7 (e.g., -$(C(O)OCH_3)_2$). In some embodiments, R^7 is heteroaryl. In some embodiments, R^7 is a bicyclic heteroaryl. In some embodiments, R^7 is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzoxazolyl). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl) or benzoxazolyl (2-benzoxazolyl). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl). In some embodiments, R^7 is benzoxazolyl (2-benzoxazolyl).

In some embodiments, R^4 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^4 is H. In some embodiments, R^4 is

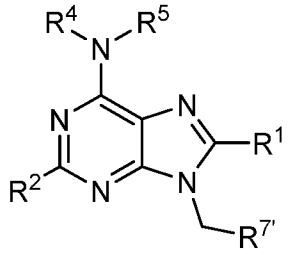
heterocyclyl (e.g., 5,6-dihydropyrimidinyl) optionally substituted with 1-5 R^8. In some embodiments, R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5 R^9. In some embodiments, R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^5 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^5 is H. In some embodiments, R^5 is heterocyclyl (e.g., 5,6-dihydropyrimidinyl) optionally substituted with 1-5 R^8. In some embodiments, R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5 R^9. In some embodiments, R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^4 is H and R^5 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5 R^9. In some embodiments, R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^4 and R^5 are taken together to form a ring optionally substituted with 1-5 R^8. In some embodiments, R^4 and R^5 are taken together to form a heterocyclyl ring (e.g., pyrrolidinyl) optionally substituted with 1-5 R^8.

In some embodiments, the compound of Formula (II) is a compound of Formula (IIa):



(IIa),

or a pharmaceutically acceptable salt thereof, wherein each R^1, R^2, R^9, R^{10}, R^C, and R^D, are defined as for Formula (I), and $R^{7'}$ is heteroaryl.

In some embodiments, R^1 is H or C_1-C_6 alkyl. In some embodiments, R^1 is H. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3).

In some embodiments, R^2 is C_1-C_6 heteroalkyl, NR^CR^D, $NR^CC(O)R^B$, halo, cycloalkyl, or heterocyclyl. In some embodiments, R^2 is NR^CR^D. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl, heterocyclyl, aryl, or heteroaryl, optionally

substituted with 1-5 R^9. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is heterocyclyl optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl (e.g., a 6-membered nitrogen-containing heterocyclyl, e.g., piperazinyl, piperidinyl, morphilinyl), each of which is optionally substituted with 1-5 R^6 (e.g., $C(O)R^B$, oxo). In some embodiments, R^6 is $C(O)R^B$ or oxo, and R^B is C_1-C_6 heteroalkyl (e.g., methoxy).

In some embodiments, R^2 is halo (e.g., chloro).

In some embodiments, R^4 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^4 is H. In some embodiments, R^4 is heterocyclyl (e.g., 5,6-dihydropyrimidinyl) optionally substituted with 1-5 R^8. In some embodiments, R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5 R^9. In some embodiments, R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^5 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^5 is H. In some embodiments, R^5 is heterocyclyl (e.g., 5,6-dihydropyrimidinyl) optionally substituted with 1-5 R^8. In some embodiments, R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5

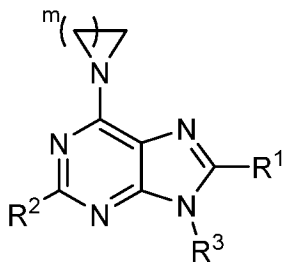
R^9. In some embodiments, R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^4 is H and R^5 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8. In some embodiments, R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5 R^9. In some embodiments, R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^4 and R^5 are taken together to form a ring optionally substituted with 1-5 R^8. In some embodiments, R^4 and R^5 are taken together to form a heterocyclyl ring (e.g., pyrrolidinyl) optionally substituted with 1-5 R^8.

In some embodiments, $R^{7'}$ is heteroaryl. In some embodiments, $R^{7'}$ is a bicyclic heteroaryl. In some embodiments, $R^{7'}$ is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzoxazolyl). In some embodiments, $R^{7'}$ is benzothiazolyl (e.g., 2-benzothiazolyl) or benzoxazolyl (2-benzoxazolyl). In some embodiments, $R^{7'}$ is benzothiazolyl (e.g., 2-benzothiazolyl). In some embodiments, $R^{7'}$ is benzoxazolyl (2-benzoxazolyl).

In some embodiments, the compound of Formula (II) is a compound of Formula (IIb):



(IIb)

or a pharmaceutically acceptable salt thereof, wherein each of R^2, R^3, R^9, R^{10}, R^C, and R^D are defined as for Formula (II), and m is 1, 2, 3, 4, or 5.

In some embodiments, R^1 is H or C_1-C_6 alkyl. In some embodiments, R^1 is H. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3).

In some embodiments, R^2 is C_1-C_6 heteroalkyl, NR^CR^D, $NR^CC(O)R^B$, halo, cycloalkyl, or heterocyclyl. In some embodiments, R^2 is NR^CR^D. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl, heterocyclyl, aryl, or heteroaryl, optionally substituted with 1-5 R^9. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-

dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

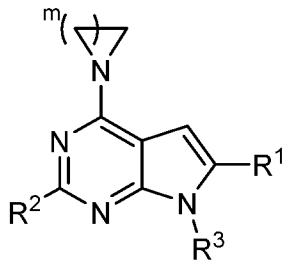
In some embodiments, R^2 is heterocyclyl optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl (e.g., a 6-membered nitrogen-containing heterocyclyl, e.g., piperazinyl, piperidinyl, morphilinyl), each of which is optionally substituted with 1-5 R^6 (e.g., $C(O)R^B$, oxo). In some embodiments, R^6 is $C(O)R^B$ or oxo, and R^B is C_1-C_6 heteroalkyl (e.g., methoxy).

In some embodiments, R^2 is halo (e.g., chloro).

I In some embodiments, R^3 is H, C_1-C_6 alkyl (e.g., CH_2), or C_1-C_6 heteroalkyl (e.g., $CH_2CH_2OCH_3$ or $CH_2CH_2N(C(O)OCH_3)_2$), substituted with 0-2 R^7. In some embodiments, R^3 is C_1-C_6 alkyl (e.g., CH_2) substituted with 1 R^7. In some embodiments, R^7 is heteroaryl. In some embodiments, R^7 is a bicyclic heteroaryl. In some embodiments, R^7 is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzoxazole). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl) or benzoxazole (2-benzoxazole). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl) or bennzoxazole (2-benzoxazole). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl).

In some embodiments, m is 2, 3, or 4. In some embodiments, m is 2. In some embodiments, m is 3 or 4. In some embodiments, m is 3. In some embodiments, m is 4.

In some embodiments, the compound of Formula (II) is a compound of Formula (IIc):



(IIc)

or a pharmaceutically acceptable salt thereof, wherein each of R^2, R^3, R^9, R^{10}, R^C, and R^D are defined as for Formula (I), and m is 1, 2, 3, 4, or 5.

In some embodiments, R^1 is H or C_1-C_6 alkyl. In some embodiments, R^1 is H. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3).

In some embodiments, R^2 is C_1-C_6 heteroalkyl, NR^CR^D, $NR^CC(O)R^B$, halo, cycloalkyl, or heterocyclyl. In some embodiments, R^2 is NR^CR^D. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl, heterocyclyl, aryl, or heteroaryl, optionally substituted with 1-5 R^9. In some embodiments, R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9. In some embodiments, one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}. In some embodiments, R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

In some embodiments, R^2 is heterocyclyl optionally substituted with 1-5 R^6. In some embodiments, R^2 is a nitrogen-containing heterocyclyl (e.g., a 6-membered nitrogen-containing heterocyclyl, e.g., piperazinyl, piperidinyl, morphilinyl), each of which is optionally substituted

with 1-5 R^6 (e.g., $C(O)R^B$, oxo). In some embodiments, R^6 is $C(O)R^B$ or oxo, and R^B is C_1-C_6 heteroalkyl (e.g., methoxy).

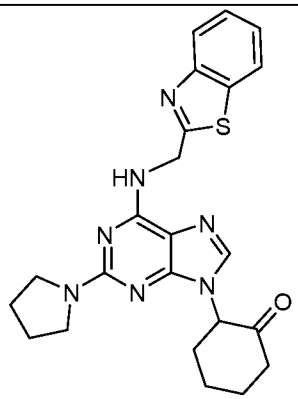
In some embodiments, R^2 is halo (e.g., chloro).

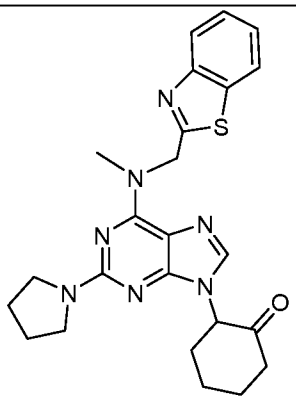
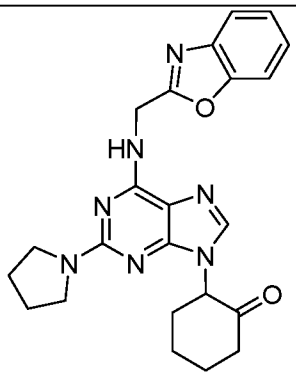
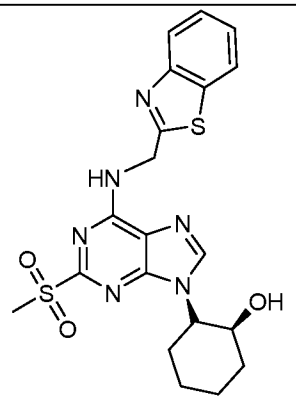
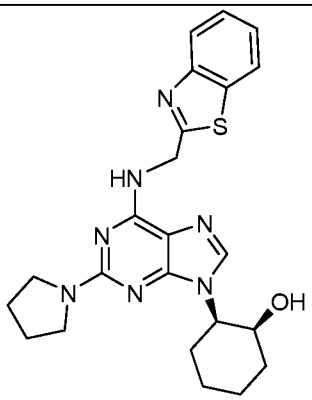
In some embodiments, R^3 is H, C_1-C_6 alkyl (e.g., CH_2), or C_1-C_6 heteroalkyl (e.g., $CH_2CH_2OCH_3$ or $CH_2CH_2N(C(O)OCH_3)_2$), substituted with 0-2 R^7. In some embodiments, R^3 is C_1-C_6 alkyl (e.g., CH_2) substituted with 1 R^7. In some embodiments, R^7 is heteroaryl. In some embodiments, R^7 is a bicyclic heteroaryl. In some embodiments, R^7 is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzoxazole). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl) or benzoxazole (2-benzoxazole). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl) or bennzoxazole (2-benzoxazole). In some embodiments, R^7 is benzothiazolyl (e.g., 2-benzothiazolyl).

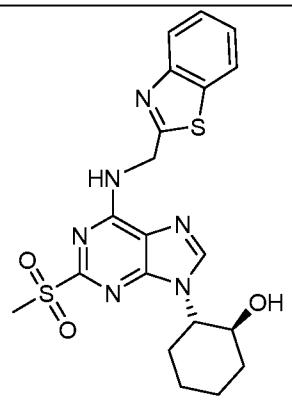
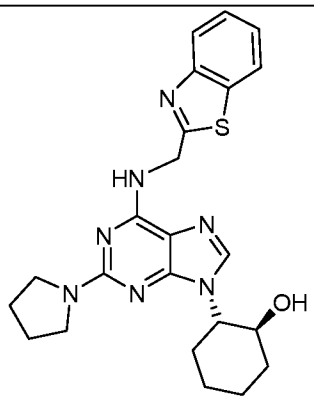
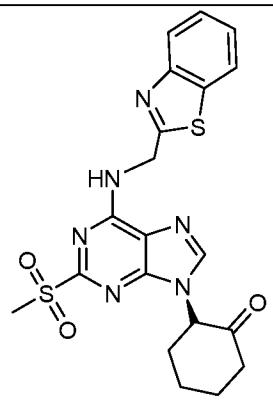
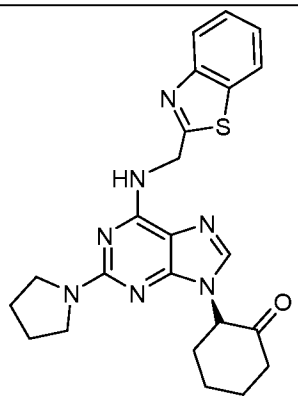
In some embodiments, m is 2, 3, or 4. In some embodiments, m is 2. In some embodiments, m is 3 or 4. In some embodiments, m is 3. In some embodiments, m is 4.

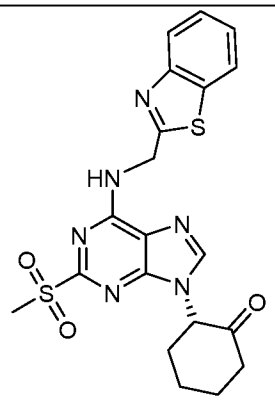
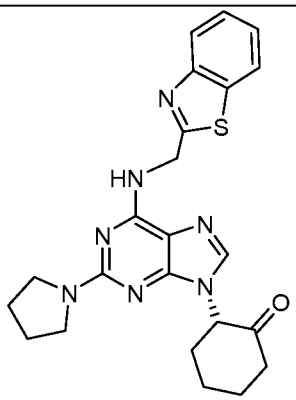
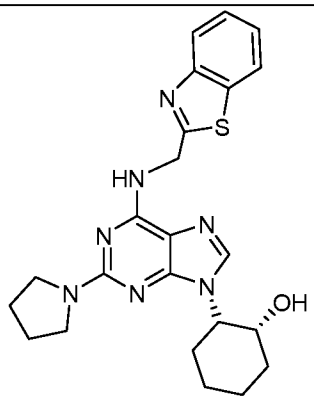
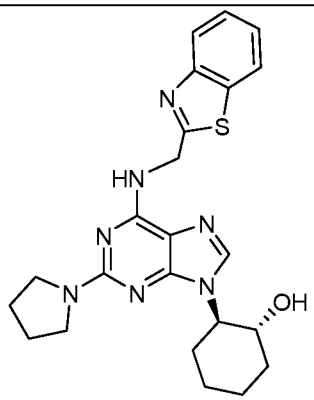
Table 1 below summarizes exemplary compounds of the invention (e.g., a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof).

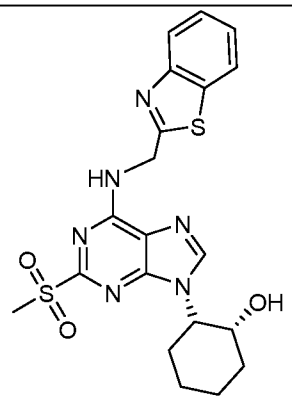
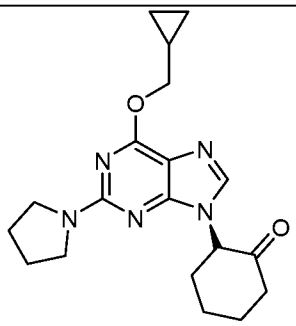
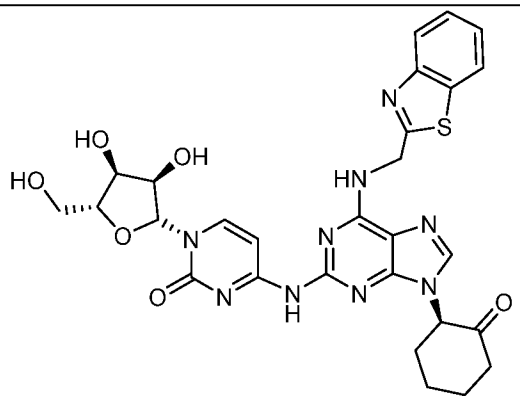
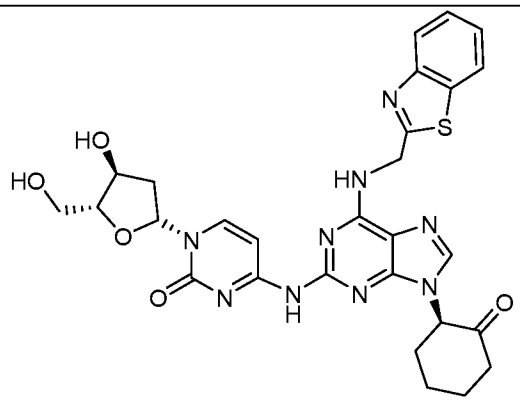
Table 1: Exemplary compounds of the invention

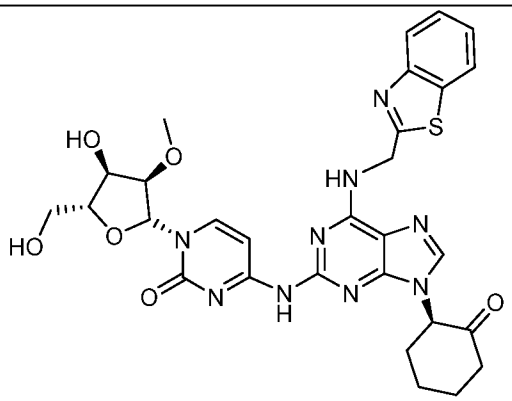
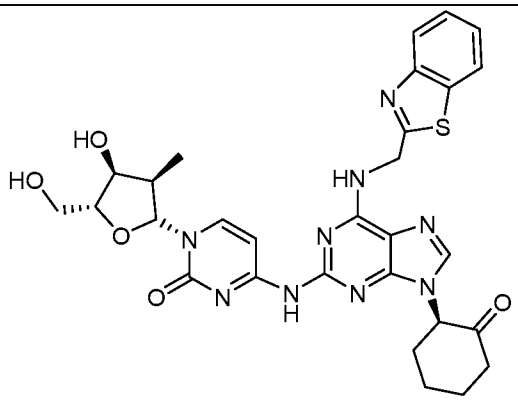
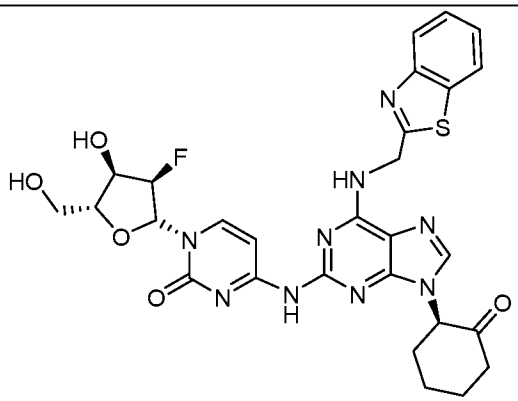
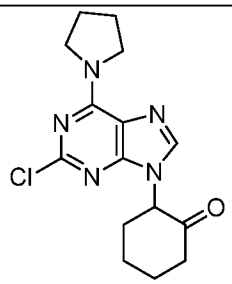
Compound Number	Structure
1	

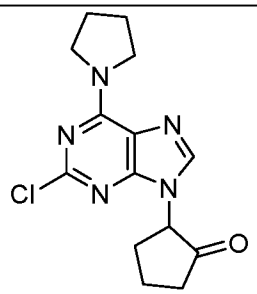
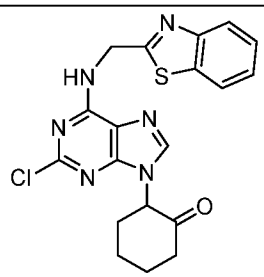
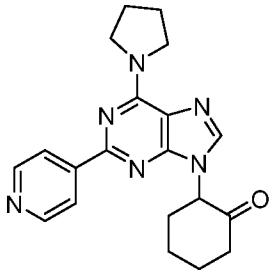
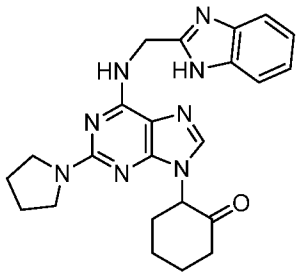
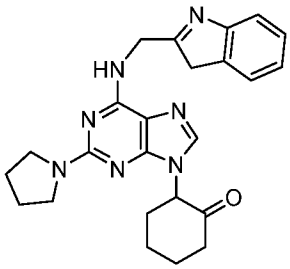
3	
4	
5	
6	

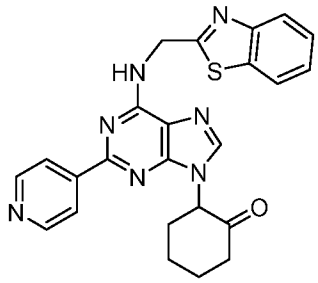
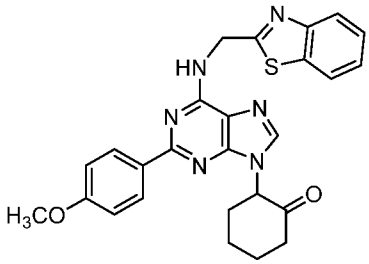
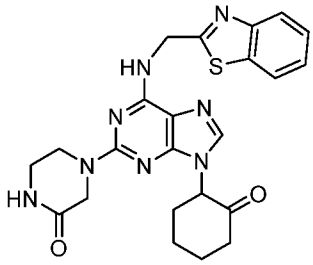
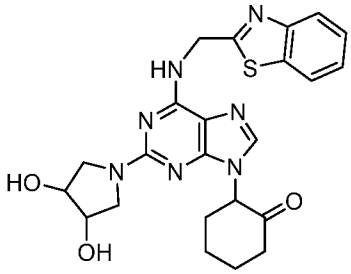
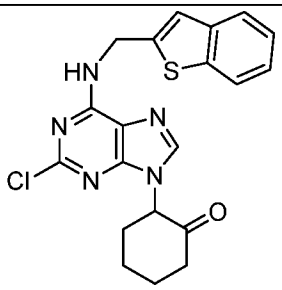
7	
8	
9	
10	

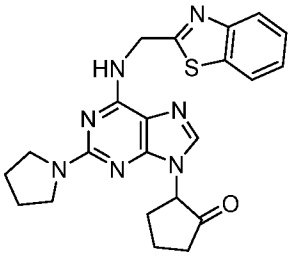
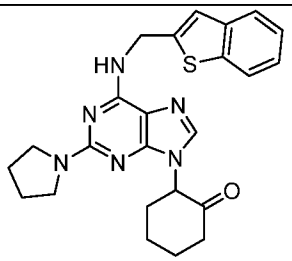
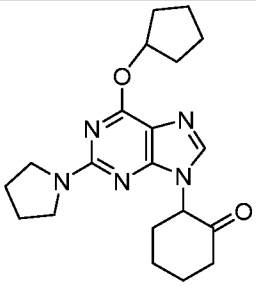
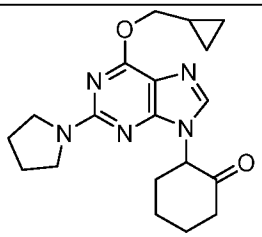
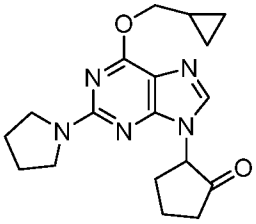
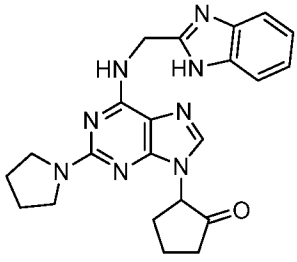
11	
12	
13	
14	

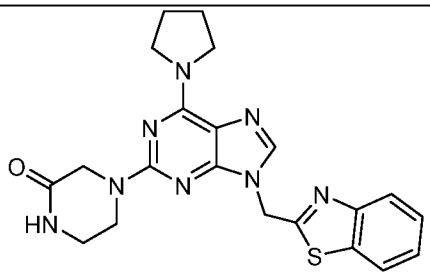
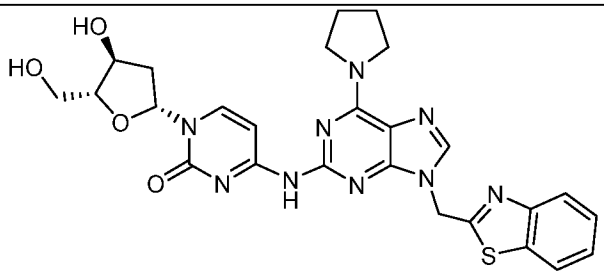
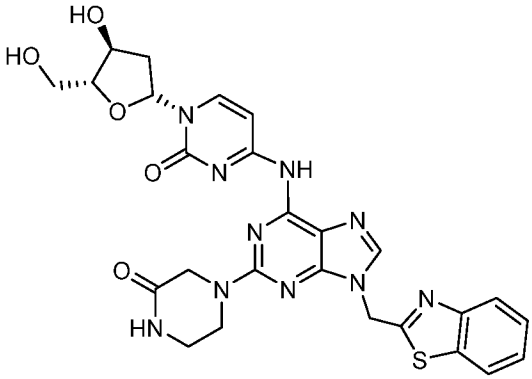
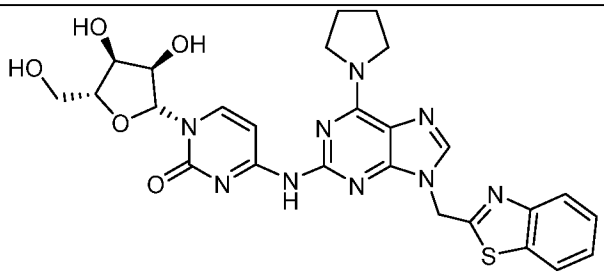
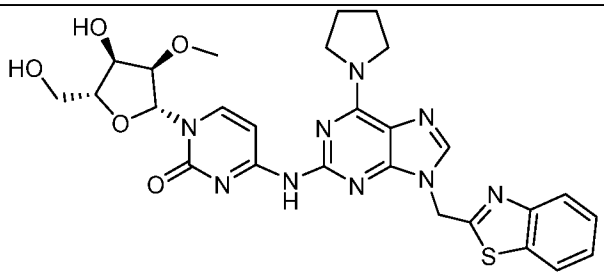
15	
16	
17	
18	

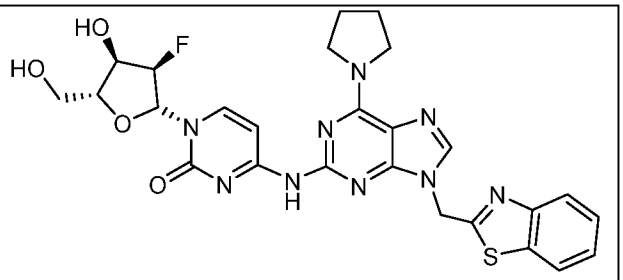
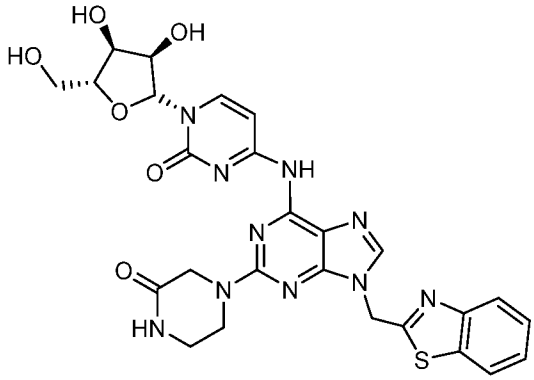
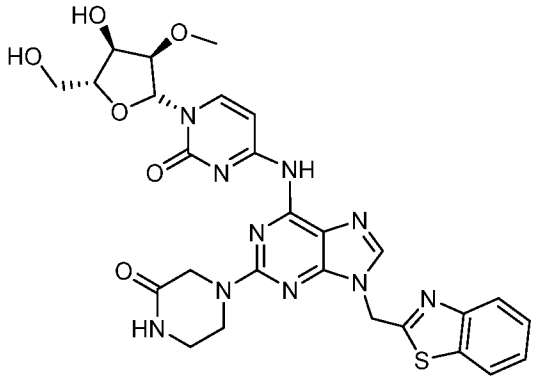
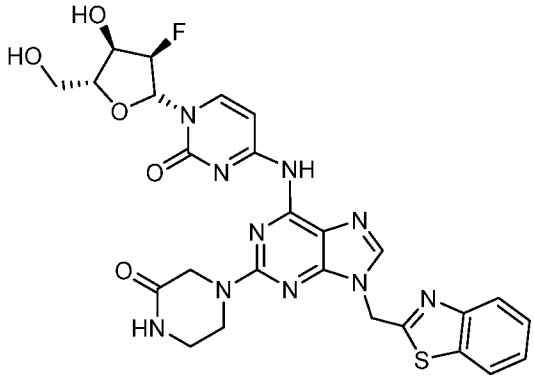
19	
20	
21	
22	

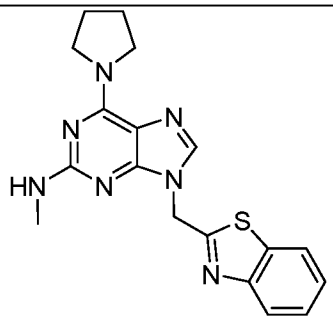
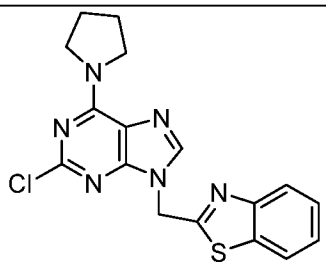
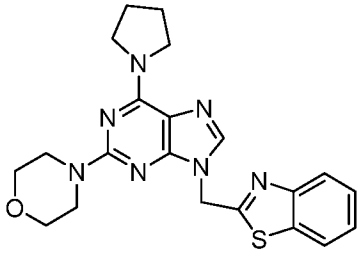
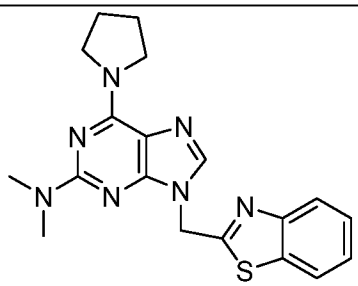
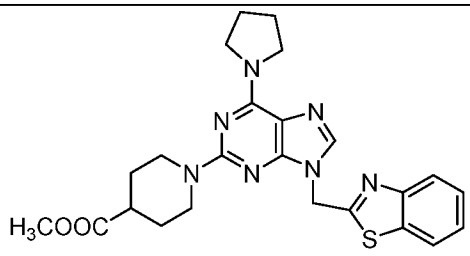
23	
24	
25	
26	
27	

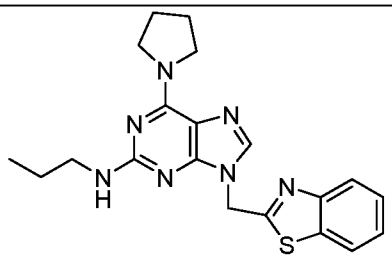
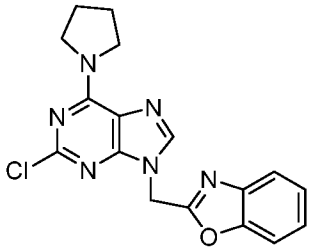
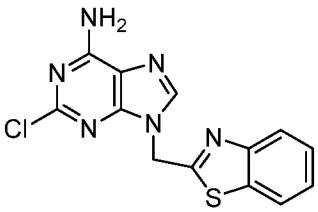
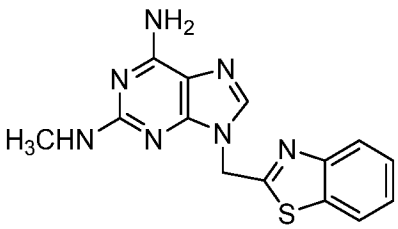
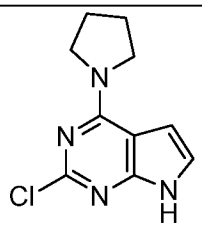
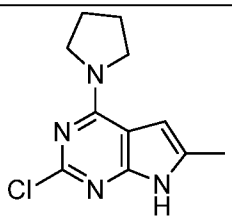
28	
29	
30	
31	
32	

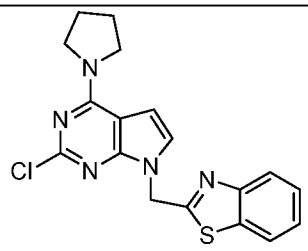
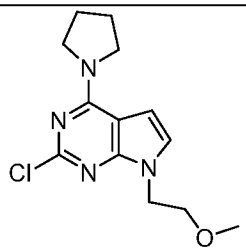
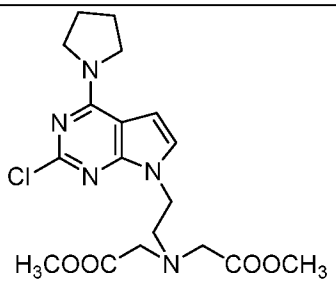
33	
34	
35	
36	
37	
38	

39	
40	
41	
42	
43	

44	
45	
46	
47	

48	
49	
50	
51	
52	

53	
54	
55	
56	
57	
58	

59	
60	
61	

The compounds provided herein may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included within the scope. Unless otherwise indicated when a compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. The compounds provided herewith may also contain linkages (e.g., carbon-carbon bonds, phosphorus-oxygen bonds, or phosphorus-sulfur bonds) or substituents that can restrict bond rotation, e.g. restriction resulting from the presence of a ring or double bond.

Phosphodiesterase 4

The present invention features compounds and compositions for the inhibition of PDE4. PDE4 is a member of the class of cyclic dinucleotide phosphodiesterases that catalyzes the

hydrolysis of cyclic AMP (cAMP), thus terminating the downstream signaling of this second messenger.

There are currently four major known gene families of PDE4 (PDE4A, PDE4B, PDE4C, and PDE4D), although to date over 25 splice variants and isoforms of PDE4 have been identified, characterized in part based on the presence or absence of an N-terminal UCR domain. Nearly all of the known PDE4 isoforms have been shown to be a substrate for a number of specific kinases and phosphatases, suggesting that the activity of PDE4 function is carefully monitored by intracellular signaling pathways. Several PDE4 enzymes also contain additional binding sites allowing macromolecular interactions with anchoring proteins such as the A-kinase anchoring proteins and the beta-arrestin. These studies suggest that PDE4 isoforms achieve precise regulation of intracellular levels of cAMP through a combination of on/off switching by kinases and phosphatases, as well as through particular localization at specific loci within cells.

The PDE4 family of enzymes has been shown to be widely distributed throughout different mammalian tissues and are present in all major organs including the brain. However, each of the four gene families of PDE4 (PDE4A, PDE4B, PDE4C, and PDE4D) has been shown to exhibit a distinct pattern of expression throughout tissues and cells. For example, while PDE4A is distributed widely, PDE4C is abundant in neuronal tissue and skeletal muscle largely absent from immune and inflammatory cells. Likewise, PDE4B is expressed throughout the nervous system, lungs, heart, and muscular tissue, while PDE4D is largely localized to the lungs, immune cells, and cerebellum (Bao, Z. et al. *Oncol Rep* (2014) 32:250-60; Eskandari, N. et al. *J Res Pharm Pract* (2015) 4:175-181). The PDE4 subtype PDE4B

In some embodiments, a compound or composition for the inhibition of PDE4 (e.g., a compound or composition described herein) is specific to one gene family of PDE4. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to one of PDE4A, PDE4B, PDE4C, or PDE4D. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to more than one of PDE4A, PDE4B, PDE4C, or PDE4D. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to one of

PDE4A, PDE4B, PDE4C, or PDE4D, with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively of one of PDE4A, PDE4B, PDE4C, or PDE4D over another of PDE4A, PDE4B, PDE4C, or PDE4D.

In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A or a variant or isoform thereof with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4B, PDE4C, or PDE4D or a variant or isoform thereof. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4B or a variant or isoform thereof with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A, PDE4C, or PDE4D or a variant or isoform thereof. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C or a variant or isoform thereof with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A, PDE4B, or PDE4D or a variant or isoform thereof. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D or a variant or isoform thereof with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A, PDE4B, or PDE4C or a variant or isoform thereof.

In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A or a variant or isoform thereof, e.g., PDE4A1, PDE4A4, PDEA6, PDEA7, PDEA8, PDEA10, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific for

more than one PDE4A or a variant or isoform thereof, e.g., PDE4A1, PDE4A4, PDE4A6, PDE4A7, PDEA8, PDEA10, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A1 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A4, PDE4A6, PDE4A7, PDEA8, PDEA10, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A4 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A1, PDE4A6, PDE4A7, PDEA8, PDEA10, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A6 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A1, PDE4A4, PDE4A7, PDEA8, PDEA10, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A7 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A1, PDE4A4, PDE4A6, PDEA8, PDEA10, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A8 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A1, PDE4A4, PDE4A6, PDEA7, PDEA10, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A10 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or

greater selectively over PDE4A1, PDE4A4, PDE4A6, PDEA7, PDEA8, or PDEA11. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4A11 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4A1, PDE4A4, PDE4A6, PDEA7, PDEA8, or PDEA10.

In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4B or a variant or isoform thereof, e.g., PDE4B1, PDE4B2, PDE4B3, PDE4B4, or PDE4B5. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific for more than one PDE4B or a variant or isoform thereof, e.g., PDE4B1, PDE4B2, PDE4B3, PDE4B4, or PDE4B5. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4B1 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4B2, PDE4B3, PDE4B4, or PDE4B5. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4B2 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4B1, PDE4B3, PDE4B4, or PDE4B5. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4B3 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4B1, PDE4B2, PDE4B4, or PDE4B5. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4B4 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater

selectively over PDE4B1, PDE4B2, PDE4B3, or PDE4B5. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4B5 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4B1, PDE4B2, PDE4B3, or PDE4B4.

In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C or a variant or isoform thereof, e.g., PDE4C1, PDE4C2, PDE4C3, PDE4C4, PDE4C5, PDE4C6, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific for more than one PDE4C or a variant or isoform thereof, e.g., PDE4C1, PDE4C2, PDE4C3, PDE4C4, PDE4C5, PDE4C6, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C1 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4C2, PDE4C3, PDE4C4, PDE4C5, PDE4C6, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C2 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4C1, PDE4C3, PDE4C4, PDE4C5, PDE4C6, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C3 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4C1, PDE4C2, PDE4C4, PDE4C5, PDE4C6, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C4 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about

a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4C1, PDE4C2, PDE4C3, PDE4C5, PDE4C6, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C5 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4C1, PDE4C2, PDE4C3, PDE4C4, PDE4C6, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C6 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4C1, PDE4C2, PDE4C3, PDE4C4, PDE4C5, or PDE4C7. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4C7 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4C1, PDE4C2, PDE4C3, PDE4C4, PDE4C5, or PDE4C6.

In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D or a variant or isoform thereof, e.g., PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound or composition described herein (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) is specific for more than one PDE4D or a variant or isoform thereof, e.g., PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D1 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II)

or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D2 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described is specific to PDE4D3 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D2, PDE4D4, PDE4D5, PDE4D6, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D4 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D2, PDE4D3, PDE4D5, PDE4D6, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D5 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D6, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D6 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D7, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D7 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D8, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula

(II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D8 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D7, or PDE4D9. In some embodiments, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is specific to PDE4D9 with at least about a 1.5-fold, about a 2-fold, about a 3-fold, about a 4-fold, about a 5-fold, about a 7.5-fold, about a 10-fold, about a 20-fold, about a 50-fold, about a 100-fold, or greater selectively over PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D7, or PDE4D8.

Methods of Treatment

The present invention features compounds and composition for the inhibition of PDE4 (e.g., compounds described herein, e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof). In some embodiments, the compounds and compositions described herein may be used to treat or prevent a disease or disorder involving aberrant function of PDE4, or a specific variant or isoform thereof (e.g., a specific isoform of PDE4A, PDE4B, PDE4C, or PDE4D). Exemplary conditions that may be treated with the compounds and compositions described herein include, but are not limited to, inflammatory diseases and neurodegenerative diseases.

Inflammatory and Autoimmune Diseases

In certain embodiments, the present invention features compounds and compositions (e.g., compounds and compositions described herein, e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) that may be used for the treatment or prevention of an inflammatory disease or an autoimmune disease. A compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein may be administered prior to the onset of, at the onset of, or after the initiation of symptoms of said inflammatory or autoimmune disease. Exemplary inflammatory conditions include, but are not limited to, multiple sclerosis, rheumatoid arthritis,

psoriatic arthritis, degenerative joint disease, spondoulo-arthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, diabetes (e.g., insulin dependent diabetes mellitus or juvenile onset diabetes), menstrual cramps, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, mucous colitis, ulcerative colitis, gastritis, esophagitis, pancreatitis, peritonitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatis (acute or chronic), multiple organ injury syndrome (e.g., secondary to septicemia or trauma), myocardial infarction, atherosclerosis, stroke, reperfusion injury (e.g., due to cardiopulmonary bypass or kidney dialysis), acute glomerulonephritis, vasculitis, thermal injury (i.e., sunburn), necrotizing enterocolitis, granulocyte transfusion associated syndrome, and/or Sjogren's syndrome. Exemplary inflammatory conditions of the skin include, for example, eczema, atopic dermatitis, contact dermatitis, urticaria, schleroderma, psoriasis, and dermatosis with acute inflammatory components. In another embodiment, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein is used to treat or prevent allergies and respiratory conditions, including asthma, bronchitis, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, and any chronic obstructive pulmonary disease (COPD).

Additionally, a compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein may be used to treat or prevent an autoimmune disease. Exemplary autoimmune diseases include, but are not limited to, organ-tissue autoimmune diseases (e.g., Raynaud's syndrome), scleroderma, myasthenia gravis, transplant rejection, endotoxin shock, sepsis, psoriasis, eczema, dermatitis, multiple sclerosis, autoimmune thyroiditis, uveitis, systemic lupus erythematosis, Addison's disease, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), and Grave's disease.

Neurodegenerative Diseases

In certain embodiments, the present invention features compounds and compositions (e.g., compounds and compositions described herein, e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) that may be used for the treatment or

prevention of neurodegenerative disease. A neurodegenerative disease may involve a central nervous system (CNS) disorder, a peripheral nervous (PNS) disorder, a neuromuscular disorder, or other disease or condition involving any aspect of the nervous system. A compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) or composition described herein may be administered prior to the onset of, at the onset of, or after the initiation of symptoms of said neurodegenerative disease. Exemplary neurodegenerative diseases include, but are not limited to, a myelopathy, an encephalopathy, central nervous system (CNS) infection, encephalitis (e.g., viral encephalitis, bacterial encephalitis, parasitic encephalitis), meningitis (e.g., spinal meningitis, bacterial meningitis, viral meningitis, fungal meningitis), Huntington's disease, Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, a mental health disorder (e.g., schizophrenia, depression, dementia), pain and addiction disorders, brain tumors (e.g., intra-axial tumors, extra-axial tumors), adult brain tumors (e.g., glioma, glioblastoma), pediatric brain tumors (e.g., medulloblastoma), cognitive impairment, genetic disorders (e.g., Huntington's disease, neurofibromatosis type 1, neurofibromatosis type 2, Tay-Sachs disease, tuberous sclerosis), headache (e.g., tension headache, migraine headache, cluster headache, meningitis headache, cerebral aneurysm and subarachnoid hemorrhage headache, brain tumor headache), stroke (e.g., cerebral ischemia or cerebral infarction, transient ischemic attack, hemorrhagic (e.g., aneurysmal subarachnoid hemorrhage, hypertensive hemorrhage, other sudden hemorrhage)), epilepsy, spinal disease (e.g., degenerative spinal disease (e.g., herniated disc disease, spinal stenosis, and spinal instability), traumatic spine disease, spinal cord trauma, spinal tumors, hydrocephalus (e.g., communicating or non-obstructive hydrocephalus, non-communicating or obstructive hydrocephalus, adult hydrocephalus, pediatric hydrocephalus, normal pressure hydrocephalus, aqueductal stenosis, tumor associated hydrocephalus, pseudotumor cerebri), CNS vasculitis (e.g., primary angiitis of the central nervous system, benign angiopathy of the central nervous system, Arnold Chiari malformation, neuroAIDS, retinal disorders (e.g., age-related macular degeneration, wet age-related macular degeneration, myopic macular degeneration, retinitis pigmentosa, proliferative retinopathies), inner ear disorders, tropical spastic paraparesis, arachnoid cysts, locked-in syndrome, Tourette's syndrome, adhesive arachnoiditis, altered consciousness, autonomic neuropathy, benign essential tremor, brain anomalies, cauda equine

syndrome with neurogenic bladder, cerebral edema, cerebral spasticity, cerebral vascular disorder, and Guillain-Barre syndrome.

Additional Agents

The present invention features compounds and compositions (e.g., compounds and compositions described herein, e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) that may be used for the inhibition of PDE4, or the treatment or prevention of a PDE4-mediated disorder in a subject, e.g., an inflammatory or neurodegenerative disease. In some embodiments of the present invention, the subject is further administered an additional agent or treatment in conjunction with a compound of a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof. In some embodiments, the additional agent may be an agent for inhibition of PDE4, or an agent for treating an inflammatory disease, an autoimmune disease, or a neurodegenerative disease. In some embodiments, the additional agent is an anti-PDE4 agent, e.g., rolipram, AN2728, E6005, roflumilast, piclamilast, mesembrenone, luteolin, ibudilast, diazepam, cilomilast, or apremilast. In some embodiments, the additional agent is an agent for treatment of an inflammatory or autoimmune disease, e.g., a steroid (e.g., prednisone) or a NSAID (e.g., naproxen or ibuprofen). In some embodiments, the additional agent is an agent for treatment of a neurodegenerative disease, e.g., a neurotransmitter (e.g., dopamine, L-dopa, acetylcholine) or a GABA agonist. In other embodiments, the additional agent is one that targets a symptom of an inflammatory disease, an autoimmune disease, or a neurodegenerative disease, e.g., an anti-nausea medication, a skin cream, a steroid, etc. Other exemplary additional agents may include, but are not limited to, a beta-adrenergic agonist (e.g., a beta2-agonist (e.g., salbutamol, epinephrine, ritodrine, procaterol, pirbuterol, isoetarine, clenbuterol, terbutaline, metaproterenol, isoproterenol, formoterol, fenoterol, or levosalbutamol)), an anticholinergic agent (e.g., an antimuscarinic agent (e.g., atropine, benzatropine, tropicamide, solifenacin, trihexyphenidyl, tiotropium, tolterodine, oxybutynin, oxitropium, orphenadrine, ipratropium, hydroxyzine, glycopyrrolate, doxylamine, diphenhydramine, dimenhydrinate, dicyclomine, chlorpheniramine, biperiden) or an antinicotinic agent (e.g., tubocurrarine, mecamylamine, bupropion, dextromethorphan, doxacurium, or hexamethonium)), a bronchodilator (e.g., salbutamol, levosalbutamol, pirbuterol, epinephrine,

ephedrine, terbutaline, salmeterol, clenbuterol, formoterol, bambuterol, or indacaterol), or another agent or combination thereof.

In some embodiments, the combination of a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and the additional agent has a synergistic or additive effect. In some embodiments, the term "additive" refers to an outcome wherein when two agents are used in combination, the combination of the agents acts in a manner equal to but not greater than the sum of the individual anti-PDE4 activity of each agent.

In some embodiments, the terms "synergy" or "synergistic" refer to an outcome wherein when two agents are used in combination, the combination of the agents acts so as to require a lower concentration of each individual agent than the concentration required to be efficacious in the absence of the other agent. In some embodiments, a synergistic effect results in a reduced in a reduced minimum inhibitory concentration of one or both agents, such that the effect is greater than the sum of the effects. A synergistic effect is greater than an additive effect. In some embodiments, the agents in the composition herein may exhibit a synergistic effect, wherein the anti-PDE4 activity at a particular concentration is greater than at least about 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 10, 12, 15, 20, 25, 50, or 100 times the anti-PDE4 activity of either agent alone.

Pharmaceutical Compositions

The present invention features compounds (e.g., compounds of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) and compositions for the inhibition of PDE4, as well as methods of treating and preventing a PDE4-mediated disease, such as an inflammatory or neurodegenerative disease. In certain embodiments, methods for treating a subject suffering from a PDE4-mediated disease (e.g., an inflammatory or neurodegenerative disease) comprise administering a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof to the subject. The methods described herein may further comprise administration of a composition of a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof combined with one or more pharmaceutically acceptable diluents, excipients, or carriers. The compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine. In certain embodiments, the compounds included in the pharmaceutical preparation may be active itself, or may be a prodrug,

e.g., capable of being converted to an active compound in a physiological setting (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof). Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into a pharmaceutically acceptable dosage form such as described below or by other conventional methods known to those of skill in the art.

The amount and concentration of compounds of the present invention (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) in the pharmaceutical compositions, as well as the quantity of the pharmaceutical composition administered to a subject, can be selected based on clinically relevant factors, such as medically relevant characteristics of the subject (*e.g.,* age, weight, gender, other medical conditions, and the like), the solubility of compounds in the pharmaceutical compositions, the potency and activity of the compounds, and the manner of administration of the pharmaceutical compositions. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of *Comprehensive Medicinal Chemistry* (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

Thus, another aspect of the present invention provides pharmaceutically acceptable compositions comprising a therapeutically effective amount or prophylacticaly effective amount of a composition comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for oral or parenteral administration, for example, by oral dosage, or by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension. However, in certain embodiments the subject compounds may be simply dissolved or suspended in sterile water. In certain embodiments, the pharmaceutical preparation is non-pyrogenic, i.e., does not elevate the body temperature of a patient.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of the compound other than directly into the central nervous system, such that it enters the patient's

system and, thus, is subject to metabolism and other like processes, for example, oral, intranasal, or subcutaneous administration.

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

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, stabilizing agent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject antagonists from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) ascorbic acid; (17) pyrogen-free water; (18) isotonic saline; (19) Ringer's solution; (20) ethyl alcohol; (21) phosphate buffer solutions; (22) cyclodextrins such as Captisol®; and (23) other non-toxic compatible substances such as antioxidants and antimicrobial agents employed in pharmaceutical formulations.

As set out above, certain embodiments of the compounds described herein may contain a basic functional group, such as an amine, and are thus capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final

isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts without limitation include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, trifluoroacetate, and laurylsulphonate salts and the like (see, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of the compound of the present invention (e.g., a compound of Formula (I) or Formula (II)). These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like (see, for example, Berge et al., *supra*).

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

The pharmaceutically acceptable carriers, as well as wetting agents, emulsifiers, lubricants, coloring agents, release agents, coating agents, sweetening, flavoring agents, perfuming agents, preservatives, antioxidants, and other additional components may be present in an amount between about 0.001% and 99% of the composition described herein. For example, said pharmaceutically acceptable carriers, as well as wetting agents, emulsifiers, lubricants, coloring agents, release agents, coating agents, sweetening, flavoring agents, perfuming agents, preservatives, antioxidants, and other additional components may be present from about 0.005%, about 0.01%, about 0.05%, about 0.1%, about 0.25%, about 0.5%, about 0.75%, about 1%, about 1.5%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 85%, about 90%, about 95%, or about 99% of the composition described herein.

Pharmaceutical compositions of the present invention may be in a form suitable for oral administration, e.g., a liquid or solid oral dosage form. In some embodiments, the liquid dosage form comprises a suspension, a solution, a linctus, an emulsion, a drink, an elixir, or a syrup. In some embodiments, the solid dosage form comprises a capsule, tablet, pill, dragée, powder, or microencapsulated dose form. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. Pharmaceutical compositions may comprise, in addition to the compounds described herein (e.g., a compound of Formula (I) or Formula (II)) or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and may optionally further comprise one or more pharmaceutically acceptable excipients, such as, for example, stabilizers (*e.g.,* a binder, *e.g.,* polymer, *e.g.,* a precipitation inhibitor, diluents, binders, and lubricants.

In some embodiments, the composition described herein comprises a liquid dosage form for oral administration, e.g., a solution or suspension. In other embodiments, the composition described herein comprises a solid dosage form for oral administration capable of being directly compressed into a tablet. In addition, said tablet may include other medicinal or pharmaceutical agents, carriers, and or adjuvants. Exemplary pharmaceutical compositions include compressed tablets (*e.g.,* directly compressed tablets), *e.g.,* comprising compounds of the present invention (e.g.,a compound of Formula (I) or Formula (II)) or pharmaceutically acceptable salts thereof.

In other embodiments, the composition described herein comprises a liquid dosage form for inhalation or intranasal administration, e.g., a spray, a solution, a nebulized formulation, or a suspension. In certain embodiments, the composition provided for inhalation or intranasal administration is provided as a solid dosage form (e.g., a powder) for inhalation or intranasal administration, which may be combined with a liquid prior to administration by a subject. In certain embodiments, said formulations may include other medicinal or pharmaceutical agents, carriers, and or adjuvants to provide certain desired properties, e.g., to aid in absorption by the lungs or nasal passages, enhance stability of the composition, or aid in solubility of the active agents in a liquid prior to administration.

Formulations of the present invention include those suitable for parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about 99 percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent. Pharmaceutical compositions of this invention suitable for parenteral administration comprise compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be

maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

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

In some cases, in order to prolong the effect of compounds of the present invention (e.g., a composition comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof), it may be desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered form of the compound of the present invention is accomplished by dissolving or suspending compound in an oil vehicle.

In some embodiments, it may be advantageous to administer the compound (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) and compositions of the present invention in a sustained fashion. It will be appreciated that any formulation that provides a sustained absorption profile may be used. In certain embodiments, sustained absorption may be achieved by combining a compound of the present invention with other pharmaceutically acceptable ingredients, diluents, or carriers that slow its release properties into systemic circulation.

Routes of Administration

The compounds and compositions used in the methods described herein may be administered to a subject in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. Exemplary routes of administration include

topical, enteral, or parenteral applications. Topical applications include but are not limited to epicutaneous, inhalation, enema, eye drops, ear drops, and applications through mucous membranes in the body. Enteral applications include oral administration, rectal administration, vaginal administration, and gastric feeding tubes. Parenteral administration includes intravenous, intraarterial, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, intrastemal, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

In some embodiments, the compositions described herein comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof are administered orally. In exemplary embodiments of the invention, the compositions described herein comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof are administered intravenously. In other embodiments, the compositions described herein comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof are administered intranasally (e.g., by administration into the nasal passage).

For intravenous, intraperitoneal, or intrathecal delivery or direct injection, the composition must be sterile and fluid to the extent that the composition is deliverable by syringe. In addition to water, the carrier can be an isotonic buffered saline solution, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

The choice of the route of administration will depend on whether a local or systemic effect is to be achieved. For example, for local effects, the composition can be formulated for topical administration and applied directly where its action is desired. For systemic, long term effects, the composition can be formulated for enteral administration and given via the digestive

tract. For systemic, immediate and/or short term effects, the composition can be formulated for parenteral administration and given by routes other than through the digestive tract.

In some embodiments, in the case of treatment of a pulmonary disease, a composition described herein (e.g., a composition of comprising a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) is delivered via inhalation or intranasally directly into the lungs or a nasal passage. In these cases, in certain embodiments, the composition may be provided as a nebulized formulation with a suitable device to enable local delivery into the lungs or nasal passage (e.g., through a spray device or an inhaler).

Dosages

The compositions of the present invention are formulated into acceptable dosage forms by conventional methods known to those of skill in the art. Actual dosage levels of the active ingredients in the compositions of the present invention (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof) may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, the route of administration, the time of administration, the rate of absorption of the particular agent being employed, the duration of the treatment, other drugs, substances, and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the subject being treated, and like factors well known in the medical arts. A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the composition required. For example, the physician or veterinarian can start doses of the substances of the invention employed in the composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable daily dose of a composition of the invention will be that amount of the substance which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the effective daily dose of a therapeutic composition may be

administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

Preferred therapeutic dosage levels are between about 0.1 mg/kg to about 1000 mg/kg (*e.g.*, about 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, 175 mg/kg, 200 mg/kg, 250 mg/kg, 300 mg/kg, 350 mg/kg, 400 mg/kg, 450 mg/kg, 500 mg/kg, 600 mg/kg, 700 mg/kg, 800 mg/kg, 900 mg/kg, or 1000 mg/kg) of the composition per day administered (e.g., orally) to a subject afflicted with the disorders described herein (e.g., an inflammatory, autoimmune, or neurodegenerative disease). Preferred prophylactic dosage levels are between about 0.1 mg/kg to about 1000 mg/kg (*e.g.*, about 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, 175 mg/kg, 200 mg/kg, 250 mg/kg, 300 mg/kg, 350 mg/kg, 400 mg/kg, 450 mg/kg, 500 mg/kg, 600 mg/kg, 700 mg/kg, 800 mg/kg, 900 mg/kg, or 1000 mg/kg) of the composition per day administered (e.g., orally) to a subject. The dose may also be titrated (e.g., the dose may be escalated gradually until signs of toxicity appear, such as headache, diarrhea, or nausea).

The frequency of treatment may also vary. The subject can be treated one or more times per day (e.g., once, twice, three, four or more times) or every so-many hours (e.g., about every 2, 4, 6, 8, 12, or 24 hours). The composition can be administered 1 or 2 times per 24 hours. The time course of treatment may be of varying duration, e.g., for two, three, four, five, six, seven, eight, nine, ten, or more days, two weeks, 1 month, 2 months, 4 months, 6 months, 8 months, 10 months, or more than one year. For example, the treatment can be twice a day for three days, twice a day for seven days, twice a day for ten days. Treatment cycles can be repeated at intervals, for example weekly, bimonthly or monthly, which are separated by periods in which no treatment is given. The treatment can be a single treatment or can last as long as the life span of the subject (e.g., many years).

Patient Selection and Monitoring

The methods of the present invention described herein entail administration of a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof for the prevention or treatment of a disease or disorder described herein. Accordingly, a patient and/or subject can be selected for treatment using a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof by first evaluating the patient and/or subject to determine whether the subject is suffering from a disease or symptom of a disease described herein (e.g., an inflammatory or neurodegenerative disease). If a subject is found to be suffering from a disease (e.g., a disease described herein, e.g., an inflammatory or neurodegenerative disease), a subsequent step may entail a determination of the severity of the symptoms of the disease using standard diagnostic protocols and methods known in the art. The subject can also be monitored, for example, subsequent to administration of a composition described herein (e.g., a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof).

In some embodiments, the subject is a mammal. In some embodiments, the subject is a human. In some embodiments, the subject has been diagnosed with a disease or disorder. In some embodiments, the subject is diagnosed with an inflammatory disease (e.g., an inflammatory disease described herein). In other embodiments, the subject is diagnosed with an autoimmune disease (e.g., an autoimmune disease described herein). In still other embodiments, the subject is diagnosed with a neurodegenerative disease (e.g., a neurodegenerative disease described herein).

In some embodiments, the subject is treatment naïve. In some embodiments, the subject has previously been treated for a disease or disorder described herein (e.g., an inflammatory, autoimmune, or neurodegenerative disease). In some embodiments, the subject is suffering from a relapsed disease or disorder described herein (e.g., an inflammatory, autoimmune, or neurodegenerative disease). In some embodiments, the subject has been treated with an anti-inflammatory agent other than a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and is suffering from a relapsed or worsening of an inflammatory disease. In some embodiments, the subject has been treated with an anti-autoimmune agent other than a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and is suffering from a relapsed or worsening of an autoimmune disease. In some embodiments, the subject has been treated with an agent known to mitigate the effects of a neurodegenerative

disease other than a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and is suffering from a relapsed or worsening of a neurodegenerative disease.

EXAMPLES

In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

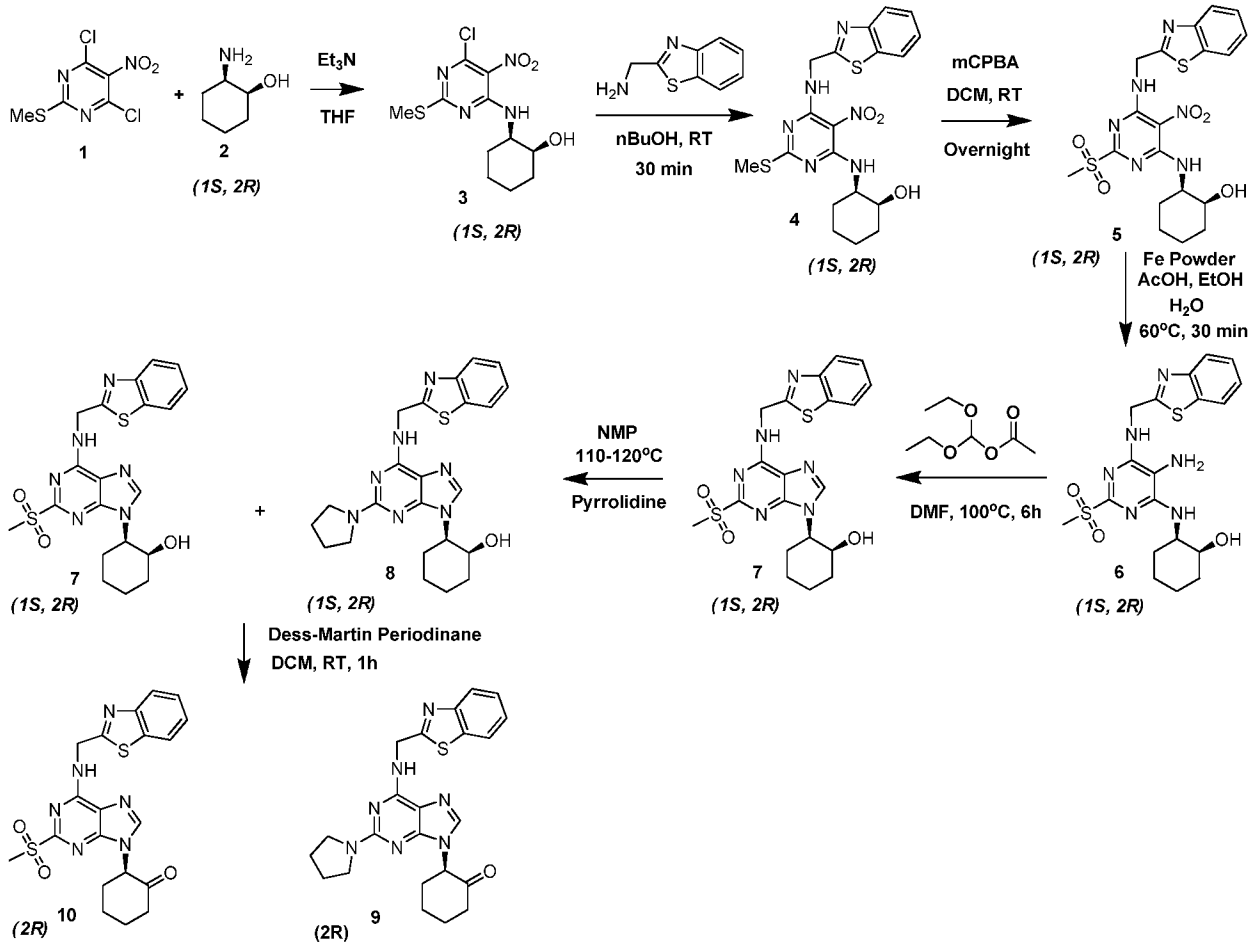
The compounds provided herein can be prepared from readily available starting materials using modifications to the specific synthesis protocols set forth below that would be well known to those of skill in the art. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in Greene *et al.*, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Example 1: Synthesis of (1S,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 5), (1S,2R)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 6), (S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-one (Compound 9) and (S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 10)

The synthesis of Compounds 5, 6, 9 and 10 were carried out according to the protocol outlined in Scheme 1 and below.

Scheme 1



Synthesis of Intermediate 3:

To a solution of pyrimidine **1** (1.5 g, 6.25 mmol) and 1*S*, 2*R*-2-amino-1-hydroxy cyclohexane **2** (1.042 g, 6.87 mmol) in THF (30 mL) was added triethylamine (1.91 mL, 13.75 mmol). The mixture was stirred at room temperature overnight, and the reaction progress was monitored by TLC. THF was evaporated to dryness, and the residue was dissolved in DCM (100 mL). The organic layer washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a crude residue. The resulting crude product was purified by silica gel column chromatography using 0-10% EtOAc in DCM to give 1.43 g of pure product intermediate **3** as light yellow solid.

Synthesis of Intermediate 4:

To a solution of intermediate **3** (1.83 g, 5.74 mmol) in n-BuOH (20 mL) was added benzothiazolemethylamine (1.13 g, 6.88 mmol) and triethylamine (2.4 mL, 17.22 mmol), and the reaction mixture was stirred at room temperature for 30 min and monitored by TLC. At the end of the reaction, the mixture was diluted with DCM (100 mL) and washed with water (2 x 75 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give crude residue, which was dried under high vacuum and purified on silica gel using 0-5% MeOH in DCM to give 2.25 g of pure product intermediate **4** as light yellow solid. **MS:** *m/z* = 447.2 $(M+H)^+$

Synthesis of Intermediate 5:

A solution of the sulfide intermediate **4** (2.2 g, 4.93 mmol) in DCM (200 mL) was cooled to 0°C and *m*-chloroperbenzoic acid (mCPBA) (77 %, 3.31 g, 14.79 mmol) was added, and the reaction mixture was stirred at room temperature overnight, at which point TLC indicated the reaction was complete. A saturated solution of Na_2SO_3 was added slowly at 0°C and the mixture was stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with DCM (50 mL), followed by washing of the combined organic layer with saturated $NaHCO_3$, drying over Na_2SO_4, and concentration under reduced pressure to give crude residue. The crude product was purified by silica gel column chromatography using 0-10% MeOH in DCM to give 2.33 g of pure product as light yellow solid. **MS:** *m/z* = 477.21 $(M-H)^+$

Synthesis of Intermediate 6:

To a solution of intermediate **5** (500 mg, 1.045 mmol) in a mixture of AcOH/EtOH /H_2O (5 : 4.5 : 0.5, 10 mL) was added Fe powder (4.67 mg, 8.36 mmol), and the reaction mixture was heated to 60-70°C for 30 min. The reaction progress was monitored by TLC, and upon completion of the reaction, the mixture was cooled to room temperature. Water (50 mL) was then added to the reaction mixture, which was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a residue that was dissolved in 5% MeOH in DCM (10 mL) and

precipitated by adding hexane (50 mL). The suspension was centrifuged and the solvents were decanted, followed by drying high vacuum to give 350 mg of pure product as light yellow sold. **MS:** *m/z* = 449.2 $(M-H)^+$

Synthesis of (1S,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 5), Intermediate 7:

To a solution of intermediate **6** (350 mg, 1.281 mmol) in DMF (10 mL) was added diethoxymethylacetate (250 mg, 1.537 mmol) in a pressure tube, and the reaction mixture was stirred at room temperature for 2h then heated to 100°C for 6 h. The reaction progress was monitored by TLC, and once complete was cooled to room temperature, diluted with DCM (25 mL), and washed with water (4 x 25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography using 0-10% MeOH in DCM to give 170 mg of the product, Compound 5. **MS:** *m/z* = 459.2 $(M+H)^+$

Synthesis of (1S,2R)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 6), Intermediate 8:

To a solution of intermediate **7** (Compound 5) (170 mg, 0.37 mmol) in NMP (2.0 mL) was added pyrrolidine (40 mg, 0.55 mmol) in a pressure vial. The reaction mixture was heated at 110-120°C for 8.0 h. Reaction progress was monitored by TLC (5% MeOH in DCM), then the reaction mixture was cooled to room temperature and diluted with DCM (25 mL) and washed with water (4 x 25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and dried under high vacuum to give the crude product, which was purified by silica gel column chromatography using 0-5% MeOH in DCM to give 100 mg mixture of Compound 6 and unreacted starting material (Compound 5), which was used for the next step.

Synthesis of Compound 9 and Compound 10:

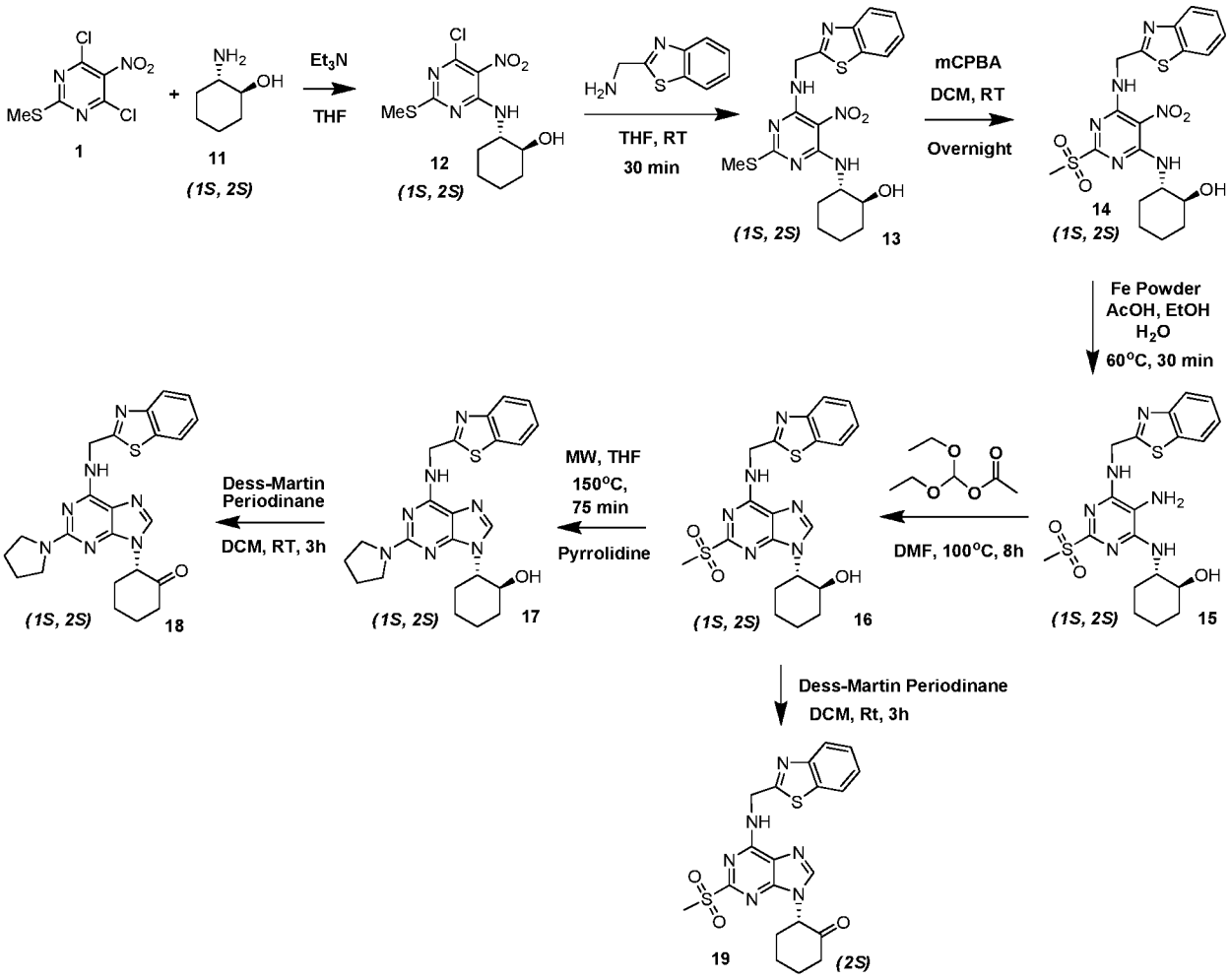
To a solution of Compound 5 and Compound 6 (100 mg, 0.222 mmol) in DCM (3.0 mL) was added Dess-Martin periodinane (100 mg, 0.235 mmol) in DCM (2.0 mL). The reaction mixture was stirred at room temperature for 1.0 h, then the reaction mixture was poured into water (20.0

mL) and extracted with DCM (2 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, then the residue was dissolved in ethyl acetate-THF (2:1, 10 mL) and 10% $Na_2S_2O_4$ solution was added to the reaction mixture and stirred at room temperature for 30 min. The organic layer was separated, washed successively with saturated solution of $NaHCO_3$ and saturated brine, dried over anhydrous Na_2SO_4, and dried under reduced pressure to achieve a crude residue that was purified by silica gel column chromatography using 0-5% MeOH in DCM. **Compound (9)**: **MS:** *m/z* = 457.2 $(M+H)^+$ 479.2 $(M+Na)^+$
Compound (10): **MS:** *m/z* = 448.3 $(M+H)^+$

Example 2: Synthesis of (1S,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 7), (1S,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 8), (S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-one (Compound 11), (S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 12)

The synthesis of Compounds 7, 8, 11, and 12 were carried out according to the protocol outlined in Scheme 2 and below.

Scheme - 2



Synthesis of Intermediate 12:

To a solution of the pyrimidine **1** (1.5 g, 6.25 mmol) and 1*S*, 2*S*-2-amino-1-hydroxy cyclohexane **11** (1.042 g, 6.87 mmol) in THF (30 mL) was added triethylamine (1.91 mL, 13.75 mmol), and the mixture was stirred at room temperature overnight. The reaction progress was monitored by TLC, and upon completion, the solvent was removed by evaporation to give a dry residue. The residue was re-dissolved in dichloromethane (100 mL), washed with water (50 mL) and brine (50 mL), and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude residue. Crude product was purified by silica gel column chromatography using 0-10% EtOAc in DCM to give 1.41 g of intermediate **12** as a light yellow solid.

Synthesis of Intermediate 13:

To a solution of intermediate 12 (1.41 g, 4.42 mmol) in THF (15 mL) was added benzothiazolemethylamine (0.87 g, 5.3 mmol) and triethylamine (1.85 mL, 13.27 mmol), and the reaction mixture was stirred at room temperature for 30 min. The reaction progress was monitored by TLC, and upon completion of the reaction, THF was evaporated under reduced pressure. The residue was dissolved in DCM (100 mL) and washed with water (2 x 75 mL) and brine (75 mL), and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude residue, which was dried under high vacuum and purified by silica gel column chromatography using 0-5% MeOH in DCM to give 2.25 g of intermediate **13** as a light yellow solid. **MS:** *m/z* = 447.2 $(M+H)^+$

Synthesis of Intermediate 14:

A solution of intermediate **13** (1.7 g, 3.81 mmol) in DCM (150 mL) was cooled to 0 °C and mCPBA (77 %, 2.29 g, 11.43 mmol) was added. The reaction mixture was stirred at room temperature overnight, and the reaction progress was monitored by TLC. Upon completion of the reaction, a saturated solution of Na_2SO_3 was added slowly at 0 °C and the mixture was stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with DCM (50 mL). The combined organic layer was then washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude residue that was purified by silica gel column chromatography using 0-10% MeOH in DCM to give 1.0 g of intermediate **14** as a light yellow solid. **MS:** *m/z* = 477.19 $(M-H)^+$

Synthesis of Intermediate 15:

To a solution of the sulfone intermediate **14** (1.0 g, 2.09 mmol) in a mixture of AcOH/EtOH /H_2O (5 : 4.5 : 0.5, 20 mL) was added Fe powder (933 mg, 16.72 mmol) and the reaction mixture was heated to 60-70 °C for 30 min. The reaction progress was monitored by TLC, and upon completion, the mixture was cooled to room temperature. The mixture was diluted with water (50 mL), and the solution was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (50 mL) followed by brine (50 mL), then dried over Na_2SO_4 and concentrated under reduced pressure to give a crude residue that was dissolved in DCM (10 mL) and precipitated by adding to hexanes (50 mL). The resulting slurry was centrifuged and the

solvents were decanted. The solid residue was dried under high vacuum to give 930 mg of pure intermediate **15** as a light yellow sold. **MS:** *m/z* = 449.2 $(M-H)^+$

Synthesis of (1S,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 7), Intermediate 16:

To a solution of intermediate **15** (900 mg, 2.0 mmol) in DMF (10 mL) was added diethoxymethylacetate (390 mg, 2.4 mmol) in a pressure tube. The reaction mixture was stirred at room temperature for 2 h, then heated at 100 °C for 8h. The reaction progress was monitored by TLC, and upon completion of the reaction, the mixture was cooled to room temperature, diluted with DCM (100 mL) and washed with water (4 x 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give crude product that was purified by silica gel column chromatography using 0-10% MeOH in DCM to give 300 mg pure Compound 7. **MS:** *m/z* = 459.3 $(M+H)^+$ 481.3 $(M+Na)^+$

Synthesis of (1S,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 8), Intermediate 17:

To a solution of Compound 7 (150 mg, 0.327 mmol) in THF (5 mL) was added pyrrolidine (120 mg, 1.68 mmol) in a microwave vial. The reaction mixture was irradiated by microwave in a reactor at 150 °C for 1.25 h. Upon indication that the reaction was complete by TLC analysis (5% MeOH in DCM), the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to give crude product, which was purified by silica gel column chromatography using 0-5% MeOH in DCM to give 130 mg of pure Compound 8. **MS:** *m/z* = 450.3 $(M+H)^+$

Synthesis of (S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 12), Intermediate 18:

To a solution of Compound 8 (80 mg, 0.177 mmol) in a DCM (3.0 mL), was added Dess-Martin periodinane (112 mg, 0.265 mmol) in DCM (2.0 mL). The reaction mixture was stirred at room temperature for 3.0 h. Reaction mixture was poured into water (20 mL) and extracted with DCM (2 x 20 mL). Organic layer was dried over $Na_2S_2O_4$ and concentrated under reduced pressure.

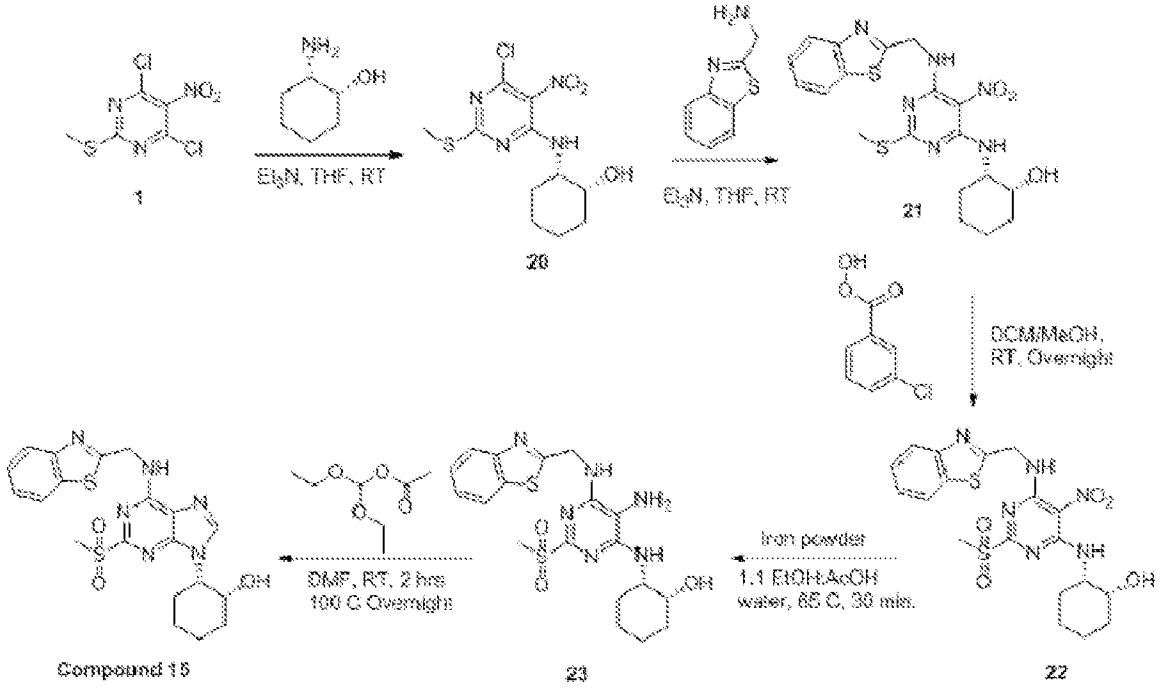
The residue was dissolved in ethyl acetate-THF (2:1, 10 mL) and 10% $Na_2S_2O_4$ solution was added to the reaction mixture and stirred at room temperature for 30 min. The organic layer was separated washed successively with saturated $NaHCO_3$, saturated brine, dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure to give crude residue. Crude product was purified on Combiflash silica gel column chromatography using 0-5% MeOH in DCM to give 7.0 mg of pure Compound 12 as a solid. **MS, m/z** 448.3 $(M+H)^+$

Synthesis of (S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-one (Compound 11), Intermediate 19:

To a solution of compound 16 (50 mg, 0.109 mmol) in a DCM (3.0 mL), was added Dess-Martin periodinane (92 mg, 0.218 mmol) in DCM (2.0 mL). Reaction mixture was stirred at room temperature for 3.0 h. Reaction mixture was poured into water (20.0 mL) and extracted with DCM (2 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in ethyl acetate-THF (2:1, 10 mL) and 10% $Na_2S_2O_4$ solution was added to the reaction mixture and stirred at room temperature for 30 min. The organic layer was separated, washed successively with saturated solution of $NaHCO_3$, saturated brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to get crude residue. Crude product was purified on Combiflash silica gel column chromatography using 0-5% MeOH in DCM to give 40.0 mg of pure Compound 11 as a solid. **MS, m/z** 457.3 $(M+H)^+$, 479.2 $(M+Na)^+$

Example 3: Synthesis of (1R,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 15)

Scheme 3



Synthesis of Intermediate 20:

4,6-dichloro-2-(methylthio)-5-nitropyrimidine (402 mg, 1.67 mmol) and 1R,2S-aminocyclohexanol (212 mg, 1.84 mmol) were dissolved and stirred in 4 mL anhydrous THF, to which was added triethylamine (0.47 mL, 3.35 mmol). The reaction was stirred at room temperature overnight and monitored by TLC (8:2 DCM:EtOAc) and LC-MS. The reaction mixture was concentrated and then partitioned between DCM and water, wherein the organic layer was extracted and the aqueous layer washed with additional DCM. The combined organic layers were washed with 10% citric acid, dried over sodium sulfate, filtered and concentrated to give intermediate **20** as a yellow foam (503.5 mg, 95% yield). **^{1}H NMR** ($CDCl_3$) δ 4.29 (m, 1H), 4.07 (m, 1H), 2.50 (m, 3H), 1.88-1.46 (m, 8H). LC-MS: (ESI- 316.86, ESI+ 318.84).

Synthesis of Intermediate 21:

Intermediate **20** (500 mg, 1.57 mmol) was dissolved in THF (4 mL) combined with 1,3-benzothiazol-2-ylmethanamine (283 mg, 1.73 mmol) and triethylamine (0.66 mL, 4.71 mmol) and stirred at room temperature. Additional benzothiazole (50 mgs) and triethylamine were added after 20 min, and upon indication that the reaction was complete by TLC and LC-MS, the

reaction was quenched with water to form a precipitate, and the solid was filtered and washed with water to provide intermediate **21** (419 mg, 60% yield). **^{1}H NMR** ($CDCl_3$) δ 8.02 (d, J=8.10 Hz, 1H), 7.86 (d, J=8.10 Hz, 1H), 7.49 (m, 1H), 7.39 (m, 1H), 5.21 (d, J=6.00, 2H), 4.43 (m, 1H), 4.04 (m, 1H), 2.45 (m, 3H), 1.85-1.41 (m, 8H).

Synthesis of Intermediate 22:

Intermediate **21** (419 mg, 0.938 mmol) was dissolved in DCM:MeOH (25:10 mL) and cooled in an ice bath, after which mCPBA (1,295 mgs, 7.51 mmol) was added and the reaction stirred at room temperature overnight. TLC (95:5 DCM:MeOH) showed conversion to the sulfone product, at which point the reaction was quenched with 5% sodium bisulfite and the organic layer washed with saturated sodium bicarbonate. The solution was then dried over sodium sulfate, filtered, concentrated, and purified by silica gel chromatography to give intermediate **22** (367 mg, 82% yield). **^{1}H NMR** ($CDCl_3$) δ 8.02 (d, J=8.40 Hz, 1H), 7.86 (d, J=8.70 Hz, 1H), 7.49 (m, 1H), 7.41 (m, 1H), 5.24 (d, J=6.00 Hz, 2H), 4.42 (m, 1H), 4.07 (m, 1H), 3.17 (m, 3H), 1.78-1.50 (m, 8H).

Synthesis of Intermediate 23:

Intermediate **22** (367 mg, 0.767 mmol) was dissolved in 9:9:1 EtOH: AcOH:H_2O, then Fe powder (350 mg, 6.13 mmol) was added and the reaction was stirred at 60 °C for 20 min. TLC (9:1 DCM:MeOH) analysis showed complete conversion to product, at which point the reaction was removed from heat and quenched with water. The product was extracted with EtOAc, and the organic layers were combined, dried over sodium sulfate, filtered and concentrated to provide intermediate **23**, which was used directly in the next step without further purification.

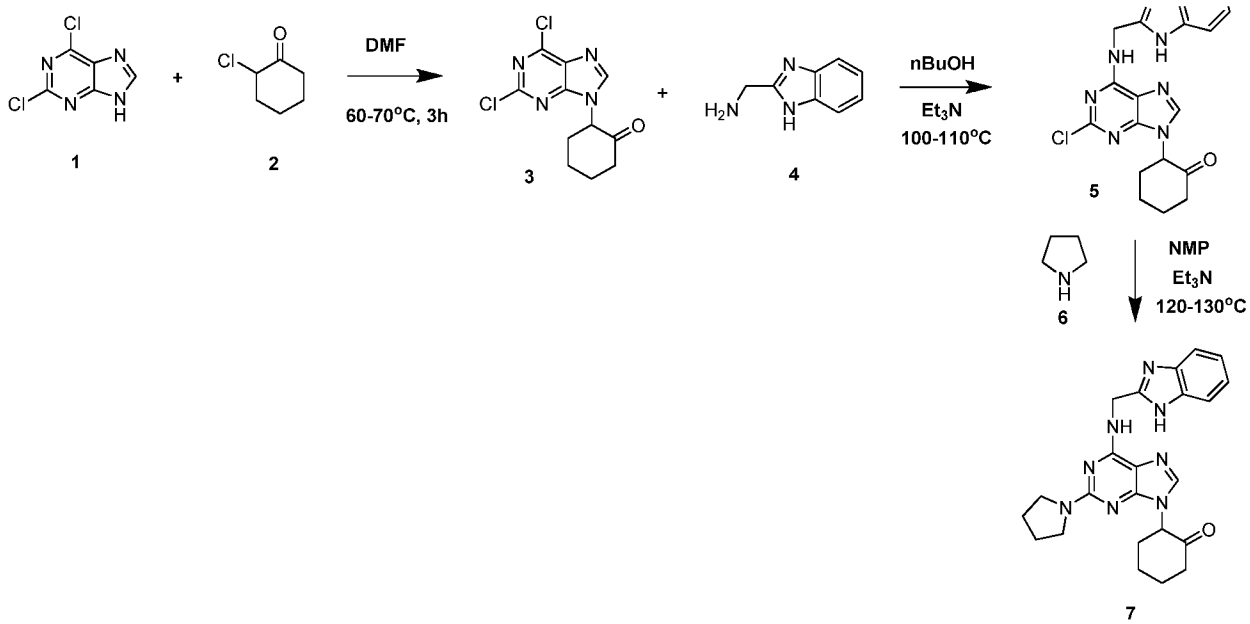
Synthesis of (1R,2S)-2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(methylsulfonyl)-9H-purin-9-yl)cyclohexan-1-ol (Compound 15):

Intermediate **23** was dissolved in DMF (6 mL) and diethoxymethylacetate (0.15 mL) was added. The reaction was stirred at room temperature for 2 h before being heated to 100 °C for 3 h, at which point TLC (9:1 DCM:MeOH) analysis indicated the reaction was complete. The reaction mixture was diluted with DCM and washed with water (3x) and brine (1x), and the organic layer

was concentrated purified by silica gel chromatography to provide Compound 15. The resulting product was further purified by recrystallization in DCM/Hexanes, resulting in pure Compound 15 (16 mg, 93% purity). **^{1}H NMR** ($CDCl_3$) δ 8.10 (s, 1H), 7.98 (d, J=8.10 Hz, 1H), 7.83 (d, J=8.40 Hz, 1H), 7.52 (m, 1H), 7.45 (m, 1H), 5.80 (s, 2H), 4.41 (m, 1H), 4.24 (m, 1H), 3.28 (m, 3H), 1.97-1.43 (m, 8H).

Example 4: Synthesis of 2-(6-(((1H-benzo[d]imidazol-2-yl)methyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 26)

Scheme 4



Synthesis of Intermediate 3:

To a solution of the purine starting material **1** (5.0 g, 26.45 mmol) in DMF (100 mL) was added K_2CO_3 (5.48g, 39.68 mmol), NaI (7.92 g, 52.91 mmol), and 2-chlorocyclohexanone (4.7 g, 31.74 mmol). The reaction was stirred at 70 °C overnight, and the progress was monitored by TLC (20% EtOAc in DCM). Upon completion of the reaction, the solvent was removed under reduced pressure, and the residue was suspended in ethyl acetate (100 mL), filtered, and the organic layer was washed with water (2 x 100 mL) and brine (100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and dried under high vacuum to give crude residue that was purified by silica gel column chromatography (0-50% ethyl acetate in hexane) to give 3.3 g of Intermediate **3** as white solid.

Synthesis of Intermediate 5:

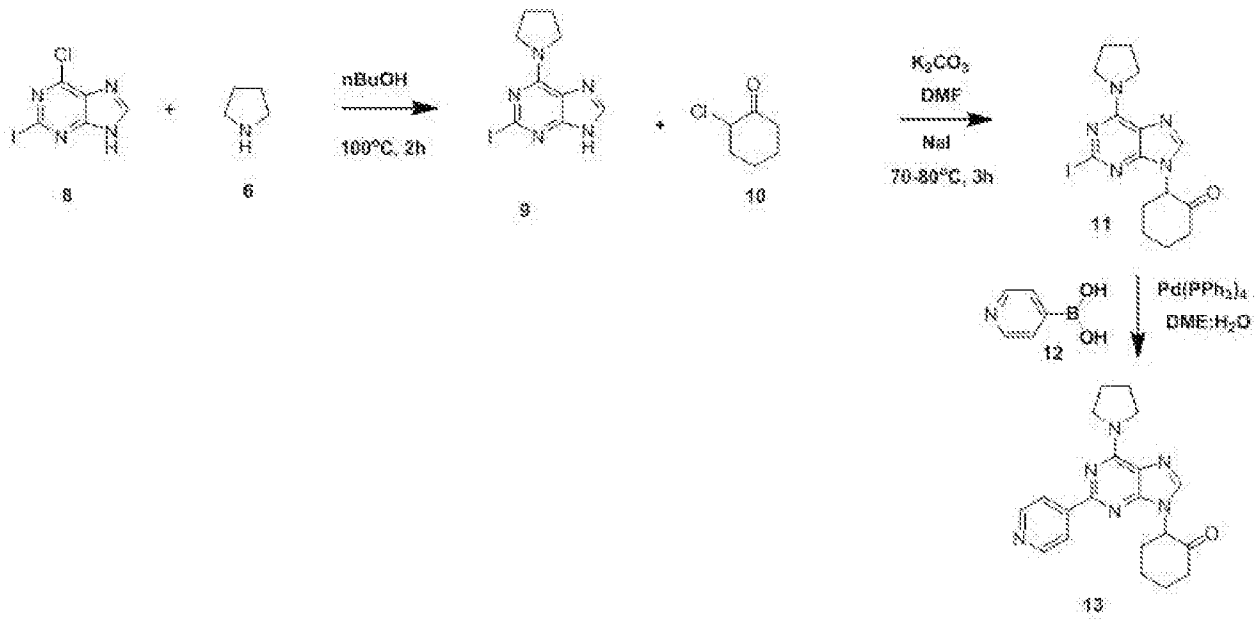
To a solution of intermediate **3** (500 mg, 1.754 mmol) in n-BuOH (5.0 mL) was added benzothiazolemethylamine (345 mg, 2.104 mmol) and triethylamine (733 µL, 5.262 mmol) in a pressure tube. The reaction mixture was heated at 100 °C for 30 min, and the reaction progress was monitored by TLC (5% MeOH in DCM). Upon completion of the reaction, the mixture was diluted with DCM (50 mL), washed with water (3 x 50 mL) and brine (50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude residue that was purified by silica gel column chromatography (0-5% MeOH in DCM) to give 570 mg of intermediate **5** as a solid.

Synthesis of 2-(6-(((1H-benzo[d]imidazol-2-yl)methyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 26), Intermediate 7

To a solution of intermediate **5** (570 mg, 1.38 mmol) in NMP (5.0 mL) was added pyrrolidine (117 mg, 1.656 mmol) and triethylamine (577 mL, 4.14 mmol) in a pressure tube, and the reaction was heated at 120 °C for 8 h. The reaction progress was monitored by TLC (5% MeOH in DCM), and upon completion, the reaction mixture was diluted DCM (50.0 mL), washed with water (4 x 50 mL) and brine (50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0-5% MeOH in DCM) to give 290 mg of pure Compound 26. **^{1}H NMR** (DMSO-d_6): δ 8.28 (1H, brs), 7.82-8.0 (2H, m), 7.72 (1H, s), 7.34-7.49 (2H, m), 5.13-5.19 (1H, m), 5.0 (2H, brs), 3.36 (3H, m), 1.69-2.68 (10H, m), 1.23-1.24 (1H, m), **MS: m/z** = 448.3 $(M+H)^+$.

Example 5: Synthesis of 2-(2-(pyridin-4-yl)-6-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 25)

Scheme 5



Synthesis of Intermediate 9:

To a solution of intermediate **8** (500 mg, 1.782 mmol) in nBuOH (5.0 mL) was added pyrrolidine (282 mg, 3.92 mmol) in a pressure tube and the reaction was heated at 100 °C for 2 h. The reaction progress was monitored by TLC (5% MeOH in DCM), and upon completion of the reaction, the mixture was cooled to room temperature. The mixture was the diluted with water extracted with 30% isopropanol in dichloromethane (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product that was purified by silica gel column chromatography (0-10% MeOH in DCM) to give 500 mg of pure intermediate **9** as a white solid.

Synthesis of Intermediate 11:

To a solution of intermediate **9** (450 mg, 1.422 mmol) in DMF (10 mL) was added K_2CO_3 (295 mg, 2.133 mmol), NaI (426 mg, 2.844 mmol), and 2-chlorocyclohexanone (226 mg, 1.706 mmol), and the reaction mixture was stirred at 70 °C for 3h. The reaction progress was monitored by TLC (5% MeOH in DCM), and upon completion, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was dissolved in DCM (50 mL), washed with water (2 x 50 mL) and brine (50 mL), and the organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a

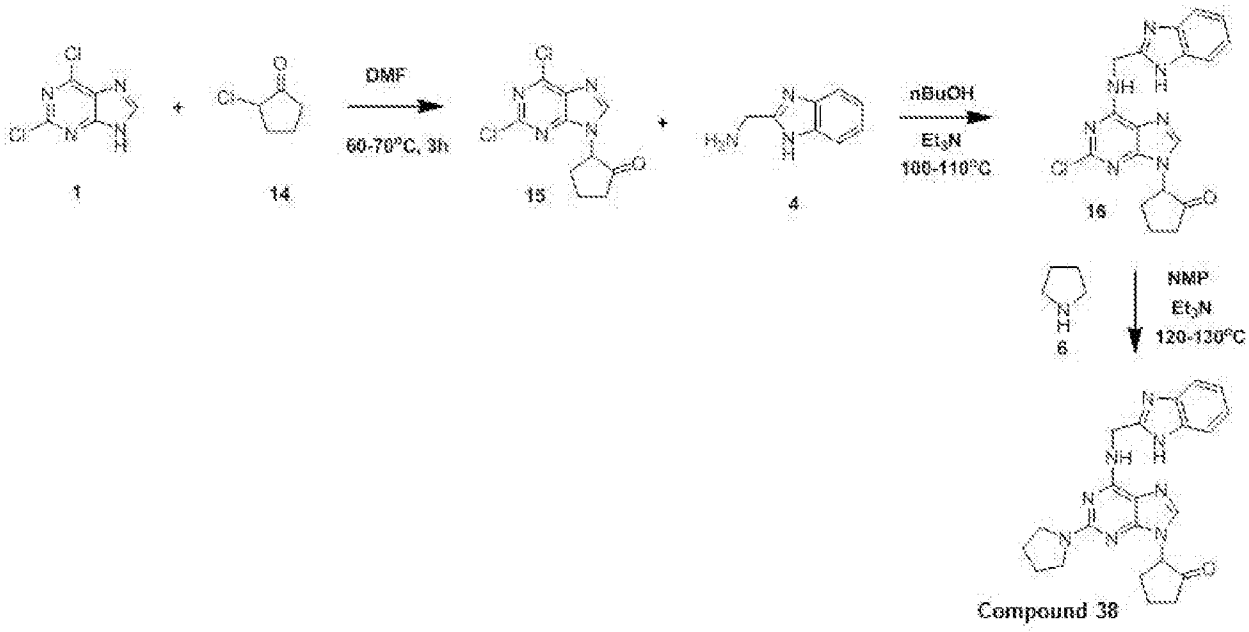
crude residue that was purified by silica gel column chromatography (0-50% ethyl acetate in hexanes) to give 445 mg of pure intermediate **11** as a white solid.

Synthesis of 2-(2-(pyridin-4-yl)-6-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 25):

To a solution of intermediate **11** (30 mg, 0.073 mmol), boronic acid **12** (14 mg, 0.109 mmol), and K_2CO_3 (28 mg, 0.197 mmol) in a mixture of dimethoxyethane (1.0 mL) and water (150 µL) was added $Pd(PPh_3)_4$ (5 mg) under argon. The reaction mixture was purged with argon and stirred under argon at 90 °C for 5h, and the reaction progress was monitored by TLC (20% EtOAc in DCM). Upon reaction completion, DCM (15 mL) was added and the mixture was washed with water (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude residue that was purified by silica gel column chromatography (0-50% EtOAc in DCM) to give 12 mg of pure Compound 25. **MS: m/z** = 363.2 $(M+H)^+$

Example 6: Synthesis of 2-(6-(((1H-benzo[d]imidazol-2-yl)methyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclopentan-1-one (Compound 38)

Scheme 6



Synthesis of Intermediate 15:

To a solution of the purine intermediate **1** (2.0 g, 10.58 mmol) in DMF (40 mL) was added K_2CO_3 (2.19g, 15.87 mmol), NaI (3.17 g, 21.16 mmol) and 2-chlorocyclopentanone (1.37 g, 11.63 mmol), and the reaction was stirred at 70 °C overnight and monitored by TLC (20% EtOAc in DCM). The mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was then dissolved in DCM (100 mL), washed with water (2 x 100 mL) and brine (100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was was purified by silica gel column chromatography (0-60% ethyl acetate in hexane) to give 1.2 g of pure intermediate **15** as a white solid.

Synthesis of Intermediate 16:

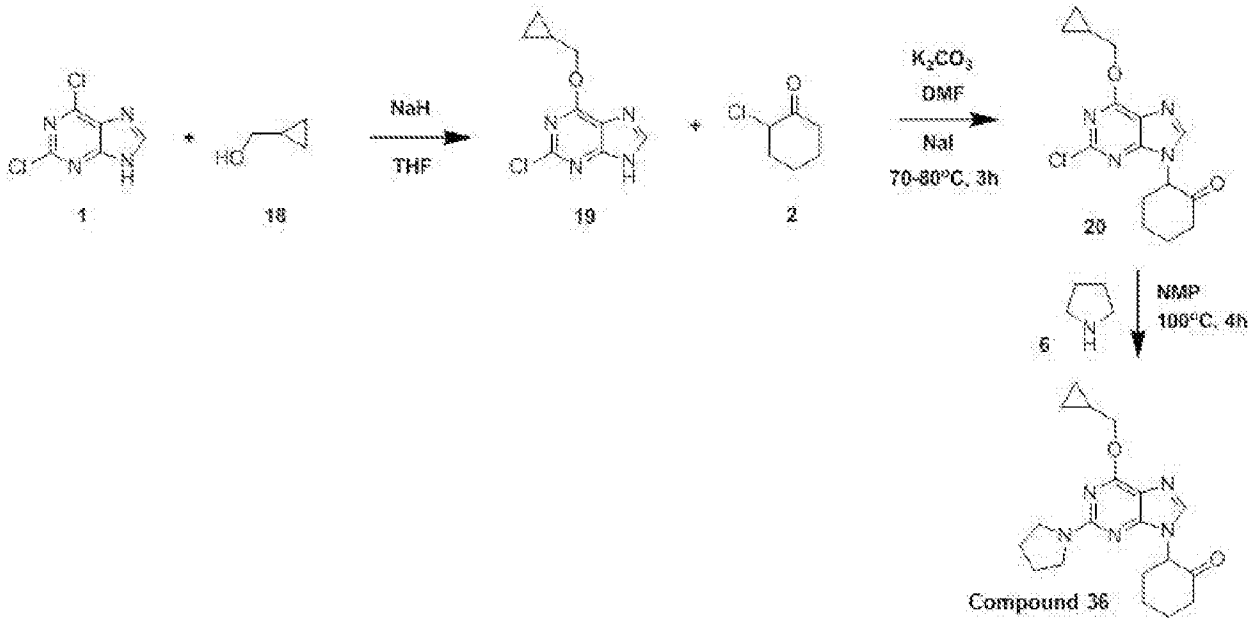
To a solution of intermediate **15** (100 mg, 0.369 mmol) in n-BuOH (1.0 mL) was added benzothiazolemethylamine (73 mg, 0.442 mmol) and triethylamine (few drops) in a pressure tube, and the reaction mixture was heated at 100 °C for 2 h and monitored by TLC (5% MeOH in DCM). The reaction mixture was then diluted with DCM (25 mL) and washed with water (3 x 20 mL) and brine (20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude residue, that was purified by silica gel column chromatography (60% EtOAc in DCM) to give 70 mg of pure intermediate **16** as white solid.

Synthesis of 2-(6-(((1H-benzo[d]imidazol-2-yl)methyl)amino)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclopentan-1-one (Compound 38):

To a solution of intermediate **16** (50 mg, 0.125 mmol) in anhydrous NMP (1.0 mL) was added pyrrolidine (15 mg, 0.187 mmol), triethylamine (two drops) in a pressure tube and the reaction was heated at 100 °C for 5 h and monitored by TLC (5% MeOH in DCM). The reaction mixture was then diluted DCM (25.0 mL), washed with water (4 x 20 mL) and brine (20 mL), and the organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product that was purified by silica gel column chromatography (0-10% MeOH in DCM) to give 7 mg of pure Compound 38. **MS:** *m/z* = 334.0 $(M+H)^+$

Example 7: Synthesis of 2-(6-(cyclopropylmethoxy)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 36)

Scheme 7



Synthesis of Intermediate 19:

THF (anhydrous, 70 mL) was slowly added under argon to NaH (3.17 g, 79.36 mmol, 60% dispersion in mineral oil), followed by the dropwise addition of cyclopropyl methanol (2.86 g, 39.68 mmol) in THF (anhydrous, 10 mL) at 0°C. After stirring at room temperature for 30 min, the reaction mixture was cooled to 0 °C and 2,6 dichloropurine (**1**) (5.0 g, 26.455 mmol) in THF (anhydrous, 20 mL) was slowly added, followed by stirring of the reaction mixture at room temperature overnight. Upon completion of the reaction as monitored by TLC (5% MeOH in DCM), the reaction mixture was cooled to 0°C and aqueous NH_4Cl solution (2.0 M, 200 mL) was added slowly dropwise. The mixture was then extracted with 30% isopropanol in DCM (2 x 250 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and the residue was dried under high vacuum overnight to give 6.92 g of pure intermediate **19** as a white solid.

Synthesis of Intermediate 20:

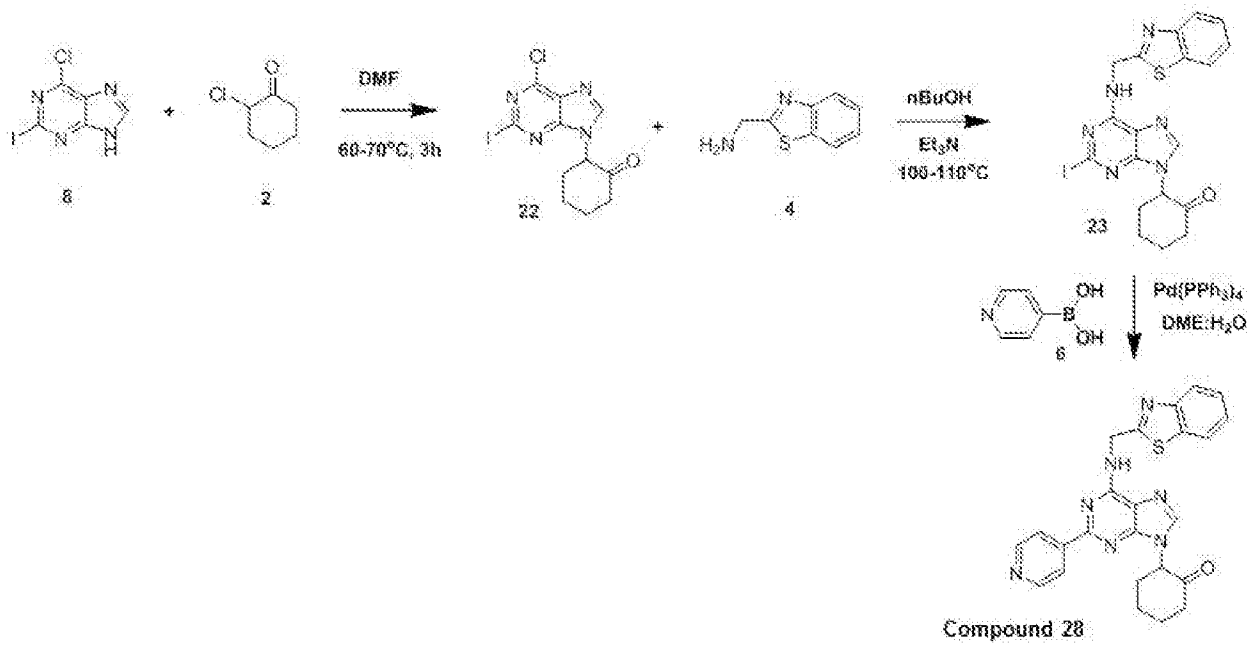
To a solution of intermediate **19** (2.0 g, 8.928 mmol) in DMF (40 mL) was added K_2CO_3 (1.85 mg, 13.392 mmol), NaI (2.676 mg, 17.856 mmol) and 2-chlorocyclohexanone (1.42 g, 10.713 mmol) in DMF (10 mL). The reaction mixture was stirred at 80 °C for 4h, and the reaction progress was monitored by TLC (20% EtOAc in DCM). Upon completion of the reaction, the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in DCM (150 mL), washed with water (3 x 100 mL) and brine (100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude residue that was purified by silica gel column chromatography (0-50% ethyl acetate in hexane) to give 1.47 g of pure intermediate **20** as a white solid.

Synthesis of 2-(6-(cyclopropylmethoxy)-2-(pyrrolidin-1-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 36):

To a solution of intermediate **20** (200 mg, 0.623 mmol) in NMP (2.0 mL) was added pyrrolidine (100 mg, 1.37 mmol) in a pressure tube, and the reaction mixture was heated at 100 °C for 4 h. The reaction progress was monitored by TLC (10% EtOAc in DCM), and upon completion, the reaction mixture was diluted DCM (25.0 mL) and washed with water (4 x 20 mL) and brine (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product that was purified by silica gel column chromatography using 0-50% EtOAc in hexanes as a gradient to give 155 mg of pure Compound 36 as a white solid. **MS:** *m/z* = 356.0 $(M+H)^+$

Example 8: Synthesis of 2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyridin-4-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 28)

Scheme 8



Synthesis of Intermediate 22:

To a solution of the purine intermediate **8** (500 mg, 1.782 mmol) in DMF (10 mL) was added K_2CO_3 (369 mg, 2.673 mmol), NaI (533 mg, 3.564 mmol), and 2-chlorocyclohexanone (283 mg, 2.138 mmol), and the reaction mixture was stirred at 70 °C for 3h. The reaction progress was monitored by TLC (5% MeOH in DCM), and upon completion, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in DCM (50 mL), washed with water (2 x 50 mL) and brine (50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude residue that was purified by silica gel column chromatography (0-50% ethyl acetate in hexane) to give 310 mg of pure intermediate **22** as a white solid.

Synthesis of Intermediate 23:

To a solution of intermediate **22** (300 mg, 0.796 mmol) in n-BuOH (3.0 mL) was added benzothiazolemethylamine (157 mg, 0.955 mmol) and triethylamine (332 µL, 2.388 mmol) in a pressure tube and the reaction mixture was heated at 100-110 °C for 3 h. The reaction progress was monitored by TLC (5% MeOH in DCM), and upon completion, the reaction mixture was diluted with DCM (25 mL) and washed with water (3 x 20 mL) and brine (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to

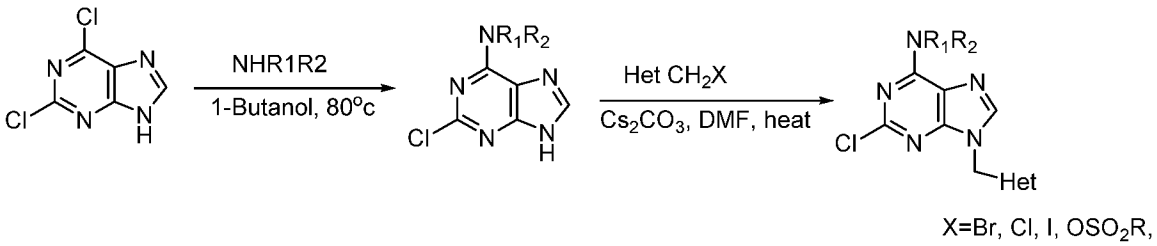
give a crude residue that was purified by silica gel column chromatography (0-5% MeOH in DCM) to give 190 mg of pure intermediate **23** as a light yellow solid.

Synthesis of 2-(6-((benzo[d]thiazol-2-ylmethyl)amino)-2-(pyridin-4-yl)-9H-purin-9-yl)cyclohexan-1-one (Compound 28):

To a solution of intermediate **23** (50 mg 0.1 mmol), boronic acid **12** (20 mg, 0.15 mmol), and K_2CO_3 (38 mg, 0.27 mmol) in a mixture of dimethoxyethane (1.0 mL) and water (150 µL) was added $Pd(PPh_3)_4$ (10 mg) under argon. The reaction mixture was purged with argon and stirred at 80 °C overnight. The reaction progress was monitored by TLC (5% MeOH in DCM), and upon completion of the reaction, DCM (25 mL) was added to reaction mixture. The mixture was washed with water (2 x 20 mL) and brine (20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude residue that was purified by silica gel column chromatography (0-5% MeOH in DCM) to give 10 mg of pure Compound 28. **MS:** *m/z* = 456.0 $(M+H)^+$

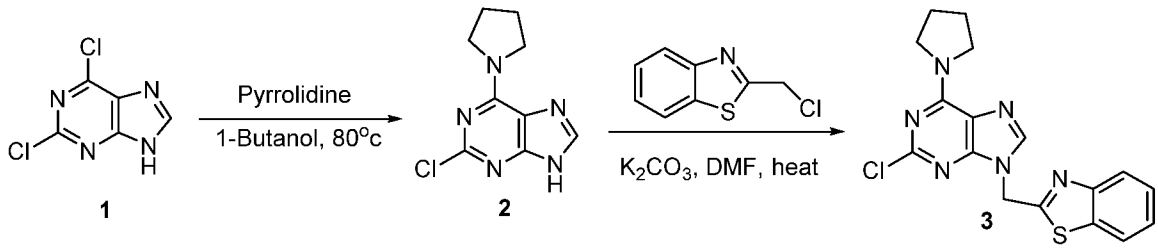
Exemplary compounds of Formula (II) were synthesized according to Scheme 9 and protocols described below.

Scheme 9



Example 9: Synthesis of 2-((2-chloro-6-(pyrrolidin-1-yl)-9H-purin-9-yl)methyl)benzo[d]thiazole (Compound 49)

Scheme 10



1 2 3

Synthesis of Intermediate 2

To a suspension of 2,6-dichloropurine (1, 0.95 g, 5.03 mmol) in 1-butanol (30 ml), pyrrolidine (0.95 ml, 11.43 mmol) was added and the suspension was stirred at room temperature. The suspension became a clear solution and was slowly heated in an oil bath at 80-85 °C for 5-6h. The reaction was monitored by TLC (DCM: MeOH 5%), and upon completion, the mixture was was cooled to room temperature and the solvent was removed under reduced pressure and co-evaporated with acetonitrile (2 x 10 mL). The residue was then stirred with water (50 mL) to remove the hydrochloride, then filtered, washed with water (10 mL) and hexanes (20 mL). The white solid was dried under high vacuum to provide intermediate **2** (5.7 g, 96%) and used for subsequent reactions without any further purification. **LC-MS**: *m/z* = 224.0 [M+1], corresponding to $C_9H_{10}ClN_5$.

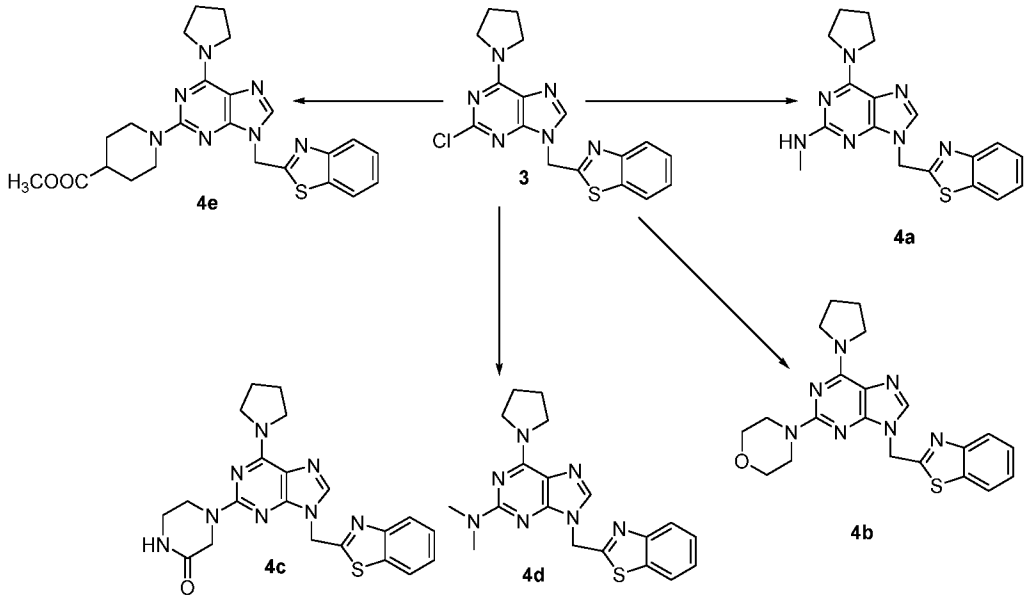
Synthesis of 2-((2-chloro-6-(pyrrolidin-1-yl)-9H-purin-9-yl)methyl)benzo[d]thiazole (Compound 49), Intermediate 3

To a mixture of intermediate **2** (112 mg, 0.5 mmol), 2-chloromethylbenzothiazole (94 mg, 0.51 mmol) and Cs_2CO_3 (196 mg) were added and dissolved in anhydrous DMF (8 mL). The slurry was heated in an oil bath at 50-55 °C under argon overnight and the reaction was found to be nearly complete by TLC analysis (DCM:MeOH 5%). The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was partitioned between water (10 mL) and DCM containing 30% isopropanol (2 x15 mL), and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and purified by silica gel chromatography using a mixture of DCM-EtOAc (0-30%) to afford Compound 19 (160 mg, 86%). **LC-MS** *m/z* = 371.2 [M+1], corresponding to $C_{17}H_{15}ClN_6S$.

Compound 49 (i.e., intermediate 3) was used for further nucleophilic substitution with different amines at the 2 position on the bicyclic core as shown in Scheme 11 below to provide exemplary

compounds of the invention, e.g., 9-(benzo[d]thiazol-2-ylmethyl)-N-methyl-6-(pyrrolidin-1-yl)-9H-purin-2-amine (Compound 48, Intermediate 4a), 4-(9-(benzo[d]thiazol-2-ylmethyl)-6-(pyrrolidin-1-yl)-9H-purin-2-yl)morpholine (Compound 50, Intermediate 4b), 4-(9-(benzo[d]thiazol-2-ylmethyl)-6-(pyrrolidin-1-yl)-9H-purin-2-yl)piperazin-2-one (Compound 39, Intermediate 4c), 9-(benzo[d]thiazol-2-ylmethyl)-N,N-dimethyl-6-(pyrrolidin-1-yl)-9H-purin-2-amine (Compound 51, Intermediate 4d), and methyl 1-(9-(benzo[d]thiazol-2-ylmethyl)-6-(pyrrolidin-1-yl)-9H-purin-2-yl)piperidine-4-carboxylate (Compound 52, Intermediate 4e).

Scheme 11



Example 10: Synthesis of 9-(benzo[d]thiazol-2-ylmethyl)-N-methyl-6-(pyrrolidin-1-yl)-9H-purin-2-amine (Compound 48), Intermediate 4a

A mixture of Intermediate **3** (50 mg) in methylamine in ethanol (33%, 2 ml), in a thick walled glass pressure reactor with Teflon screw cap (with Chemraz O ring), was heated in an oil bath at 110-115 ^{o}C under stirring overnight. The reaction mixture was allowed to cool and crystals separated on standing at RT for a couple of days. The crystals separated were collected and dried to afford pure Compound 48 (35 mg, 71%); **LC-MS** *m/z* = 366.0 [M+1], corresponding to $C_{18}H_{19}N_7S$.

Example 11: Synthesis of 4-(9-(benzo[d]thiazol-2-ylmethyl)-6-(pyrrolidin-1-yl)-9H-purin-2-yl)morpholine (Compound 50), Intermediate 4b

To a solution of Intermediate **3** (30 mg) in a thick walled glass pressure reactor with a Teflon screw cap (with Chemraz O ring) was added morpholine (1 mL) was added and the mixture was heated in an oil bath at 90 ^{o}C and stirred overnight. The reaction progress was monitored by TLC analysis (DCM: MeOH 2.5%), and the reaction mixture was concentrated extracted and processed as described for Compound 48, and purified by silica gel chromatography using DCM-MeOH (0-15%) to afford Compound 50 (21 mg, 61%); **LC-MS** *m/z* = 422.0 [M+1]. corresponding to $C_{21}H_{23}N_7OS$.

Example 12: Synthesis of 4-(9-(benzo[d]thiazol-2-ylmethyl)-6-(pyrrolidin-1-yl)-9H-purin-2-yl)piperazin-2-one (Compound 39), Intermediate 4c, and 9-(benzo[d]thiazol-2-ylmethyl)-N,N-dimethyl-6-(pyrrolidin-1-yl)-9H-purin-2-amine (Compound 51), Intermediate 4d

To a solution of Intermediate **3** (25 mg) in DMF (0.7 ml) in a thick walled glass pressure reactor topped with a Teflon screw cap (with Chemraz O ring) was added 2-piperazinone (15 mg), and the reaction was heated in an oil bath at 100-105 ^{o}C with stirring overnight. The reaction progress was monitored by TLC, and upon completion, the mixture was allowed to cool. The mixture was poured onto water (5 mL), followed by extraction in DCM (2 x 10 ml) and washing of the combined organic layers with brine. The residue was dried under high vacuum and purified by silica gel chromatography using DCM-MeOH (0-10%) to afford Compound 39 (7 mg); **LC-MS** *m/z* = 435.2 [M+1], corresponding to $C_{21}H_{22}N_8OS$; and Compound 51 (7 mg); **LC-MS** *m/z* = 435.2 [M+1], corresponding to $C_{21}H_{22}N_8OS$.

Example 13: Synthesis of methyl 1-(9-(benzo[d]thiazol-2-ylmethyl)-6-(pyrrolidin-1-yl)-9H-purin-2-yl)piperidine-4-carboxylate (Compound 52) Intermediate 4e

Following a similar protocol described for Compound 39 and Compound 51, Compound 52 was prepared using methyl piperidine-4-carboxylate for substitution to provided the desired product in a 60% yield. **LC-MS**: *m/z* = 478.0 [M+1], corresponding to $C_{24}H_{27}N_7O_2S$

Example 14: Synthesis of 2-Chloro-6-(Pyrrolidin-1-yl)-7-Deazapurine (Compound 57)

To a solution of 2, 6-dichloro-7-deazapurine (200 mg, 1 mmol) 1-butanol (5ml) was added at room temperature, followed by the slow addition of stirring pyrrolidine (0.2 ml, 2.3 mmol). The reaction was stirred for 3 h at room temperature until TLC analysis (DCM: EtOAc 7:3) indicated it was complete. The reaction mixture was concentrated, co-evaporated with acetonitrile, and treated with hexanes. The resulting solid was filtered, washed water and hexanes, and purified by silica gel chromatography to provide pure Compound 57 in high purity, **LC-MS:** *m/z* = 223.2 [M+1], corresponding to $C_{10}H_{11}ClN_4$

Example 15: Synthesis of 2-Chloro-6-(Pyrrolidin-1-yl)-8-Methyl-7-Deazapurine (Compound 58)

This compound was prepared following a similar protocol as that presented for Compound 57, except that the starting material used was 2,6-dichloro-8-methyl-7-deazapurine. Briefly, 2,6-dichloro-8-methyl-7-deazapurine (50 mg, 0.25 mmol) was suspended in 1-butanol (3 mL), and DCM (2 mL) was added dropwise until the suspension became a clear solution at room temperature. Pyrrolidine (0.55 mmol) was then added slowly, and the reaction was stirred overnight until TLC analysis (DCM: MeOH 2.5%) indicated it was complete. The mixture was concentrated and the residue dissolved in DCM (20 mL), and the resulting solution was washed with water (2 x 3 mL) to remove the hydrochloride. The solution was then dried over anhydrous Na_2SO_4 and purified by silica gel column chromatography to afford Compound 58 (55 mg, 94% yield); **LC-MS** *m/z* = 237.1 [M+1], corresponding $C_{11}H_{13}ClN_4$.

Example 16: Phosphodiesterase inhibition assay

The phosphodiesterase inhibition assay is performed using the PDE-Glo Phosphodiesterase Assay kit (Promega; Cat. No. V1361) and PDE4B1 enzyme (*(BPS Bioscience, 60041).* The assay is designed to evaluate the inhibitory effects of compounds on PDE reaction between pure PDE4B1 and a cyclic nucleotide substrate (cAMP). The principle of the assay is based on the assumption that remaining cAMP after PDE reaction can bind and release an active Protein kinase A subunit which then catalyzes phosphorylation of the PKA substrate leading to a reduction in ATP level (present in the detection buffer). Finally, luciferase activity can be

measured by adding Kinase-Glo reagent where luminescent signal produced is indirectly related to the activity of PDE4B1.

Procedure:

1. Active PDE4B1 and PDE-Glo assay kit reagents were thawed on ice and the following working solutions were prepared.
    a) 6.66 ng/ul PDE4B1 in 1X PDE-Glo buffer on ice
    b) 2uM cAMP substrate solution in 1X PDE-Glo Reaction Buffer at room temperature
    c) 1X PDE-Glo Termination Buffer with a final concentration of 2mM IBMX solution at room temperature
    d) 1X PDE-Glo detection solution with Protein Kinase A (Prepare immediately before use)
    e) Kinase-Glo reagent by adding Kinase-Glo Buffer to Kinase-Glo Substrate at room temperature
2. Compound dilutions were prepared from 10 mM stocks dissolved in DMSO in a 96 well plate.
3. 1 µl of each compound and DMSO were added to labeled quadruplicate wells in a 384 well assay plate.
4. 1.5 µl of 6.66 ng/µl PDE4B1 was added to all wells (final concentration 10 ng/well), and the plate was thoroughly mixed by centrifugation and incubated at RT for 30 min.
5. 2.5 µl of 2 µM cAMP was added to each well, and the plate was thoroughly mixed by centrifugation and incubated at RT for 15 min.
6. 2.5 µl of 1X Termination buffer (with IBMX) was added to all wells, and the plate was thoroughly mixed by centrifugation.
7. 2.5 µl of 1X Detection solution (with Protein Kianse A) was added to all wells, and the plate was mixed thoroughly by centrifugation and incubated at RT for 20min.
8. 10 µl of Kinase Glo reagent was added to all wells, and the plate was mixed well by shaking and incubated at RT in the dark for 10 min, followed by measurement of luminescence in the plate reader.
9. The raw luminescence data was plotted, and the % inhibition was calculated using the formula:

$$100 - \left\{ \frac{\text{raw value from compound added well}}{\text{average value of enzyme only wells}} \right\} X\ 100$$

10. The IC_{50} was then determined by plotting the results in XLfit.

The results for compounds evaluated in these assays are shown below in Table 2, wherein "A" refers to an IC_{50} less than 100 nM, "B" refers to an IC_{50} between 100 nM and 500 nM, "C" refers to an IC_{50} between 500 nM and 1 μM, "D" refers to an IC_{50} between 1 μM and 5 μM, and "E" refers to an IC_{50} greater than 5 μM. For percent inhibition at 5 μM, "L" refers to a value greater than 85%, "M" refers to a value between 60% and 85%, "N" refers to a value between 35% and 60%, "O" refers to a value between 15% to 35%, and "P" refers to a value between 0% and 15%. In both cases, "ND" refers to a value that was not determined.

Table 2: PDE4B1 inhibition data for exemplary compounds

Compound Number	PDE4B1 IC_{50} (human)	% Inhibition (5 μM)	Compound Number	PDE4B1 IC_{50} (human)	% Inhibition (5 μM)
1	D	M	**13**	B	ND
3	C	L	**14**	D	ND
4	E	M	**15**	A	ND
5	D	ND	**22**	ND	N
6	E	ND	**23**	ND	N
7	B	ND	**24**	ND	M
8	D	ND	**25**	ND	M
9	C	ND	**26**	ND	N
10	D	ND	**27**	ND	N
11	A	ND	**28**	ND	M
12	D	ND	**29**	ND	M

Compound Number	PDE4B1 IC_{50} (human)	% Inhibition (5 μM)
30	ND	M
31	ND	N
32	ND	M
33	ND	M
34	ND	M
35	ND	M
36	D	M
37	ND	N
39	ND	M
40	E	M
48	E	ND
49	ND	M

Compound Number	PDE4B1 IC_{50} (human)	% Inhibition (5 μM)
50	ND	M
51	ND	M
52	ND	M
53	ND	M
54	ND	N
55	ND	N
56	ND	M
57	D	M
58	ND	M
59	ND	P
60	ND	N
61	ND	N

In certain cases, the IC_{50} values of exemplary compounds of the invention were determined to gauge selectivity of the compounds against various PDE4 isoforms in comparison with a control. Table 3 summarizes the results of these assays, using the same grading scheme as that outlined above for Table 2.

Table 3: Comparison of activity of exemplary compounds against PDE4 isoforms

Compound No.	PDE4 Isoform (IC_{50}, nM)						
	PDE4B1	**PDE4B2**	**PDE4D1**	**PDE4D2**	**PDE4D3**	**PDE4D7**	**Cat domain**
1	B	B	B	B	ND	ND	ND
7	B	E	ND	ND	ND	E	ND

11	A	B	ND	ND	D	D	A
15	A	B	ND	ND	D	D	A
Rolipram	A	B	ND	ND	ND	ND	B

Example 17: TNF-α in vitro assay

Peripheral Blood Mononuclear Cells (PBMCs) were suspended in RPMI complete medium (RPMI 1640, 10 % fetal bovine serum, 100 $U \cdot mL^{-1}$ penicillin, 100 mg mL^{-1} streptomycin, 2 mM L-glutamine) and counted. 50, 000 cells were added to each well of a 96-well flat-bottom plate and incubated at 37°C for 1 h. After 1 hour of incubation, exemplary compounds were added at different concentrations to each test well, and the plate was incubated for 1 h at 37°C. Cells were then stimulated with 10ng/ml lipopolysaccharide (LPS) and incubated for 18 h at 37°C. Then supernatants were collected after centrifuging the cells to detect TNF-α released into the media by performing ELISA using the Human TNF ELISA kit (*BD Biosciences*) according to the manufacturer's instructions. Finally the absorbance at 450 nm from each well and extrapolated using a standard curve to obtain absolute values. The data was plotted and EC_{50} values were calculated in XLfit and are summarized in Table 4 below. In Table 4, "A" refers to an EC_{50} of 50 nM or less, "B" refers to an EC_{50} greater than 50 nM and less than 100 nM, "C" refers to an EC_{50} greater than 100 nM and less than 1 μM, "D" refers to an EC_{50} greater than 1 μM and less than 5 μM, and "E" refers to an EC_{50} greater than 5 μM.

Table 4:

Compound Number	**Anti-TNF EC_{50} (human)**
7	C
11	A
15	B

Example 18: Metabolic stability in liver microsomes and S9 fractions

Exemplary compounds (100 μM) were incubated with liver microsomes (M) or S9 fractions (S9) from human, rabbit, rat, or mouse samples for various time periods at 37°C. The reactions were initiated with 20mM NADPH and quenched with addition of 1ml acetonitrile. The supernatant was collected after snap freezing and centrifuging @ 4°C for 5 min followed by analysis in HPLC. The data was plotted and the half-life values ($T_{1/2}$) were calculated in Xlfit and are summarized in Table 5 below. In Table 5, "A" refers to a $T_{1/2}$ of greater than 6 hrs; "B" refers to $T_{1/2}$ of less than 6 hrs and more than 1 hr; "C" refers to a $T_{1/2}$ of less than 1 hr and more than 0.5 hr; "D" refers to a $T_{1/2}$ of less than 0.5 hr.

Table 5:

Compound Number	Human		Monkey		Dog		Rat	
	S9	M	S9	M	S9	M	S9	M
11	B	A	B	B	C	B	A	A
15	B	A	B	B	B	B	B	A

Example 19: Serum/plasma stability

Exemplary compounds (100 μM) were incubated with either rabbit, rat, or mouse serum for various time periods at 37°C. The reactions were quenched with addition of 1ml acetonitrile. The supernatant was collected after snap freezing and centrifuging @ 4°C for 5 min followed by analysis in HPLC. The data was plotted and the half-life values ($T_{1/2}$) were calculated in Xlfit.

EQUIVALENTS

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this disclosure has been described with reference to specific aspects, it is apparent that other aspects and variations may be devised by others skilled in the art without departing from the true spirit and scope of the disclosure. The appended claims are intended to be construed to include all such aspects and equivalent variations. Any patent, publication, or other disclosure material, in whole or in part,

that is said to be incorporated by reference herein is incorporated herein only to the extent that the incorporated material does not conflict with existing definitions, statements, or other disclosure material set forth in this disclosure. As such, and to the extent necessary, the disclosure as explicitly set forth herein supersedes any conflicting material incorporated herein by reference.

While this disclosure has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the disclosure encompassed by the appended claims.

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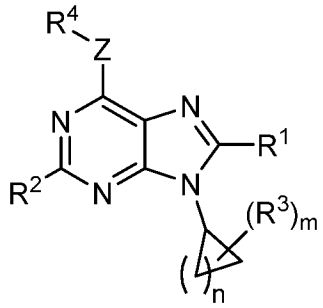
CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or NR^5;

R^1 is H, C_1-C_6 alkyl, or C_1-C_6 heteroalkyl;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, $C(O)R^A$, $C(O)OR^B$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^A$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, hydroxyl, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^6;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, $C(O)R^A$, $C(O)OR^B$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^A$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, hydroxyl, oxo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7;

R^4 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $C(O)OR^A$, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8;

R^5 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8;

wherein R^4 and R^5 may be taken together to form a ring optionally substituted with 1-5 R^8;

each of R^6 and R^7 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$,

$S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, oxo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^9;

R^8 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, oxo, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9;

each of R^A, R^B, R^C, R^D, and R^E is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9;

or wherein R^C and R^D are taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl ring, optionally substituted with 1-5 R^9;

R^9 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, hydroxyl, halo, oxo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted optionally substituted with 1-5 R^{10};

R^{10} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, halo, hydroxyl, or cycloalkyl;

R^{11} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, halo, cyano, hydroxyl, or cycloalkyl;

n is 1, 2, 3, 4, 5, 6;

m is 0, 1, 2, 3, 4, 5, or 6; and

p is 0, 1, or 2.

2. The compound of claim 1, wherein R^1 is H.

3. The compound of claim 1, wherein R^2 is C_1-C_6 alkyl, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

4. The compound of claim 1, wherein R^2 is NR^CR^D, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

5. The compound of claim 1, wherein R^2 is $S(O)_pR^E$, R^E is C_1-C_6 alkyl (e.g., CH_3), and p is 2.

6. The compound of claim 1, wherein R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9.

7. The compound of claim 6, wherein one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$) or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}.

8. The compound of claim 7, wherein R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

9. The compound of claim 1, wherein R^2 is heterocyclyl, optionally substituted with 1-5 R^6.

10. The compound of claim 9, wherein R^2 is a nitrogen-containing heterocyclyl, (e.g., a 5- or 6-membered nitrogen-containing heterocyclyl, e.g., pyrrolidinyl, piperidinyl, piperazinyl, e.g., pyrrolidinyl), each of which is optionally substituted with 1-5 R^6.

11. The compound of claim 1, wherein R^2 is halo (e.g., chloro).

12. The compound of claim 1, wherein R^2 is aryl (e.g., phenyl) or heteroaryl (e.g., pyridyl), each of which is optionally substituted with 1-5 R^6.

13. The compound of claim 1, wherein R^3 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $C(O)R^B$, $S(O)_pR^E$, halo, hydroxyl, or oxo, wherein each alkyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-6 R^7.

14. The compound of claim 1, wherein R^3 is hydroxyl or oxo.

15. The compound of claim 1, wherein R^3 is hydroxyl or oxo and n is 3 or 4.

16. The compound of claim 1, wherein R^3 is hydroxyl or oxo, n is 3 or 4, and m is 1.

17. The compound of claim 1, wherein Z is O.

18. The compound of claim 1, wherein Z is O and R^4 is C_1-C_6 alkyl (CH_2) or heterocyclyl (e.g., cyclopentyl), optionally substituted with 1-5 R^8.

19. The compound of claim 1, wherein Z is NR^5.

20. The compound of claim 1, wherein R^4 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8.

21. The compound of claim 1, wherein R^4 is H or C_1-C_6 alkyl (e.g., H or CH_3).

22. The compound of claim 1, wherein Z is NR^5 and R^5 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, or heteroaryl, wherein each alkyl, heteroalkyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8.

23. The compound of claim 22, wherein Z is NR^5 and R^5 is C_1-C_6 alkyl (e.g., -CH_2-), optionally substituted with 1-5 R^8.

24. The compound of claim 1, wherein Z is NR^5 and R^5 is C_1-C_6 alkyl (e.g., -CH_2-) substituted with 1 R^8.

25. The compound of claim 1, wherein R^8 is heterocyclyl or heteroaryl, wherein each heterocyclyl or heteroaryl is optionally substituted optionally substituted with 1-5 R^9.

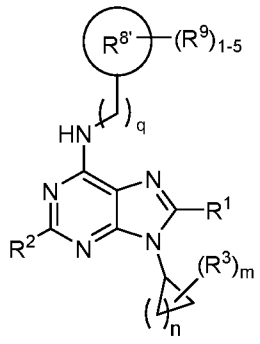
26. The compound of claim 1, wherein R^8 is heteroaryl (e.g., monocyclic or bicyclic heteroaryl).

27. The compound of claim 1, wherein R^8 is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzofuranyl, benzoxazolyl, benzothiophenyl, indolyl, or benzoimidazolyl).

28. The compound of claim 1, wherein R^8 is benzothiazolyl.

29. The compound of claim 19, wherein R^4 and R^5 are taken together to form a heterocyclyl ring (e.g., a 5-membered heterocyclyl ring, e.g., pyrrolidinyl).

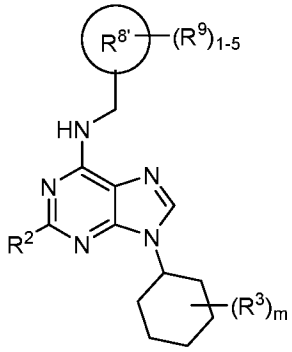
30. The compound of claim 1, wherein the compound is a compound of Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein each R^1, R^2, R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, n, and p are defined as for Formula (I), $R^{8'}$ is heteroaryl, and q is 0, 1, 2, or 3.

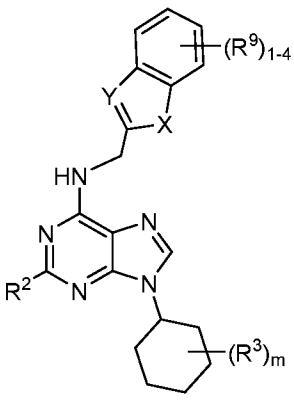
31. The compound of claim 1, wherein the compound is a compound of Formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein each R^2, R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I), and $R^{8'}$ is a nitrogen-containing bicyclic heteroaryl.

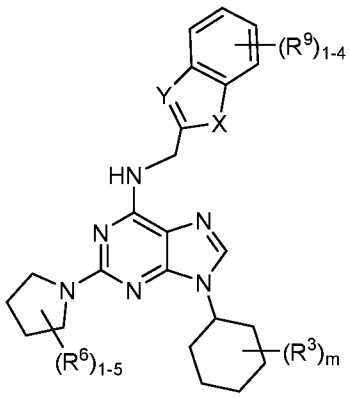
32. The compound of claim 1, wherein the compound is a compound of Formula (Ic):



(Ic)

or a pharmaceutically acceptable salt thereof, wherein each R^2, R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I), X is O, NH, CH_2, or S, and Y is N or CH.

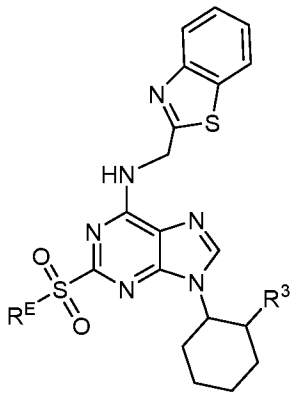
33. The compound of claim 1, wherein the compound is a compound of Formula (Id):



(Id)

or a pharmaceutically acceptable salt thereof, wherein each R^3, R^6, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I), X is O, NH, CH_2, or S, and Y is N or CH.

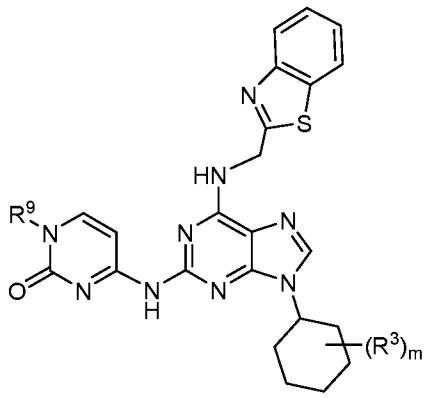
34. The compound of claim 1, wherein the compound is a compound of Formula (Ie):



(Ie)

or a pharmaceutically acceptable salt thereof, wherein each R^3, R^7, R^9, R^{10}, R^A, R^B, R^C, R^D, R^E, m, and p are defined as for Formula (I).

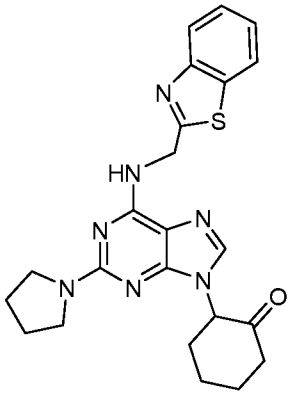
35. The compound of claim 1, wherein the compound is a compound of Formula (If):



(If)

or a pharmaceutically acceptable salt thereof, wherein each R^3, R^7, R^9, R^{10}, and m are defined as for Formula (I).

36. The compound of claim 1, wherein the compound is selected from: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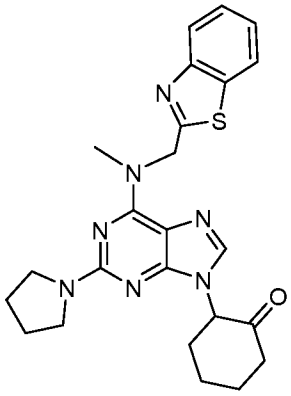
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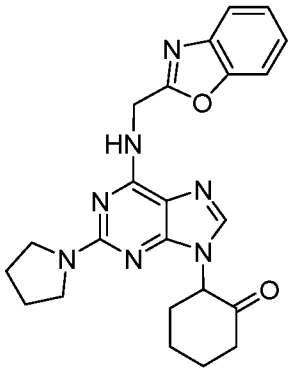
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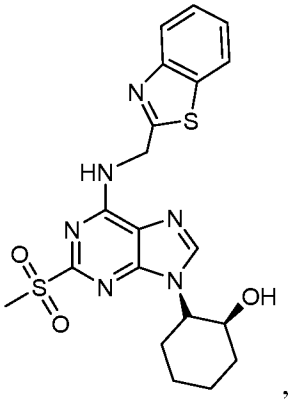
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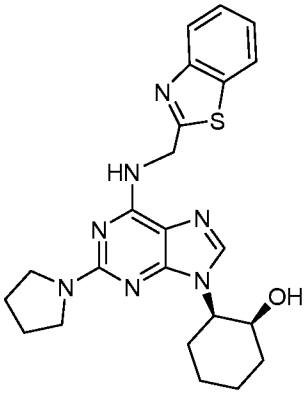
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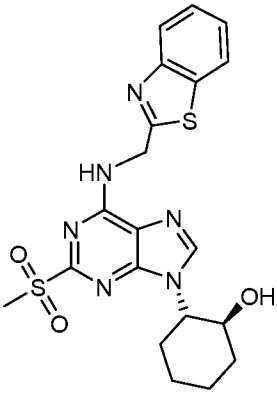
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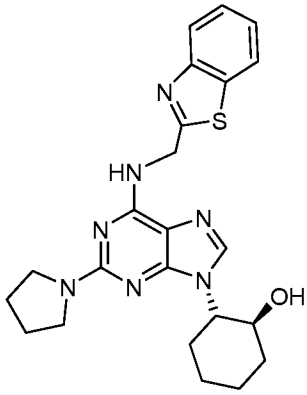
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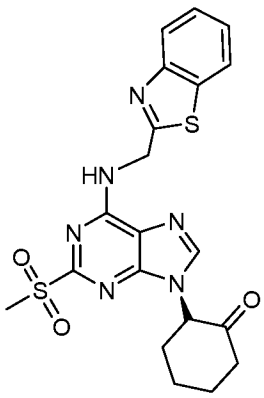
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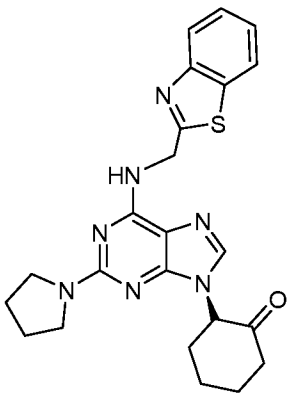
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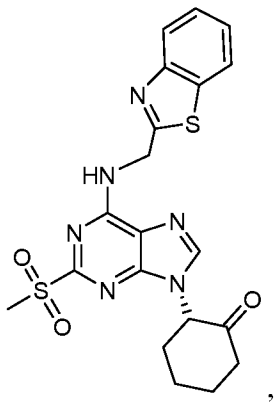
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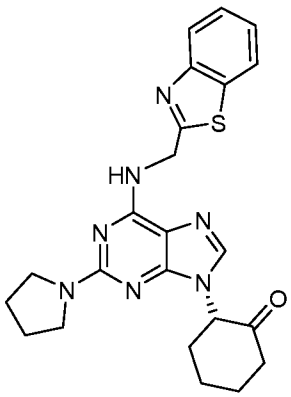
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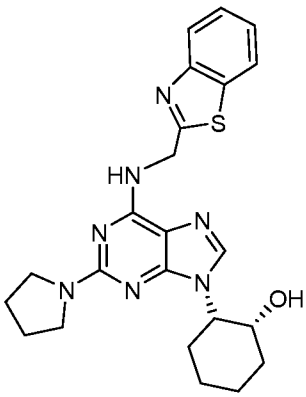
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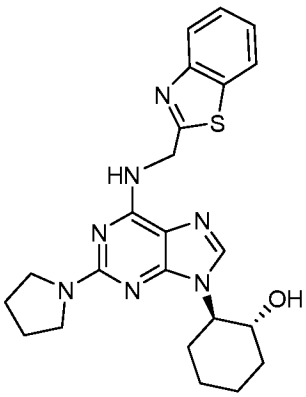
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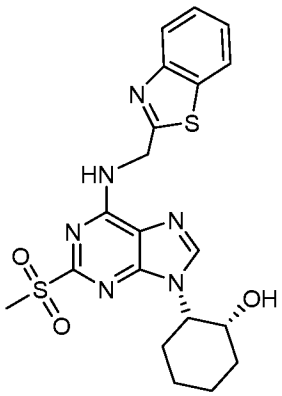
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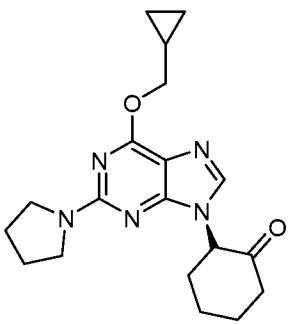
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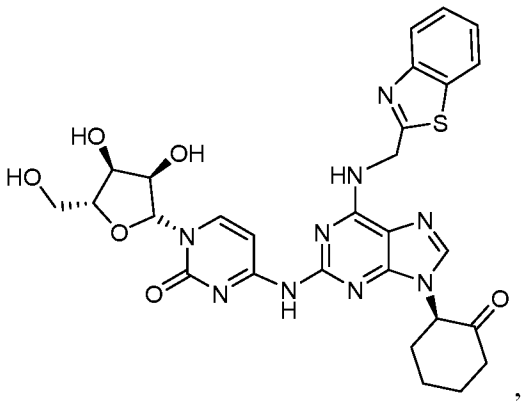
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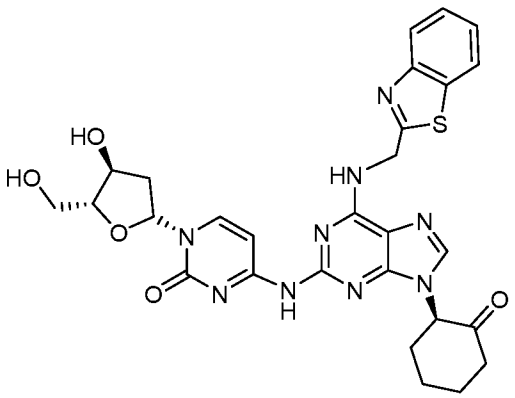
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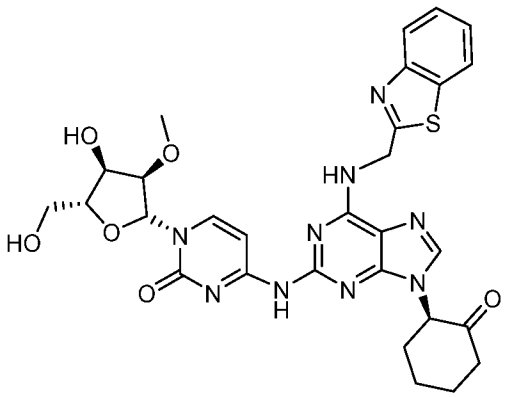
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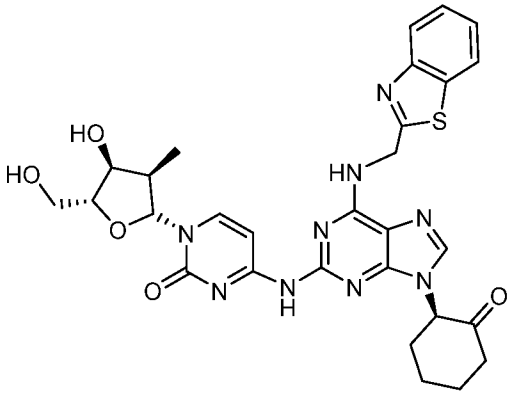
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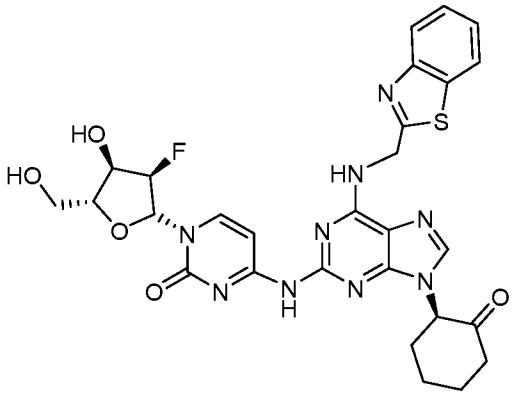
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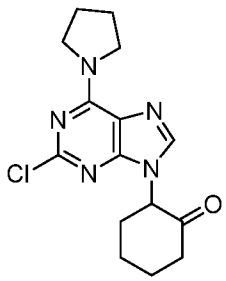
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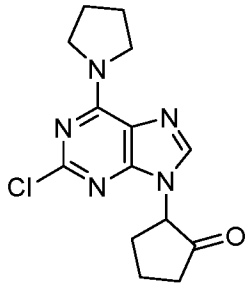
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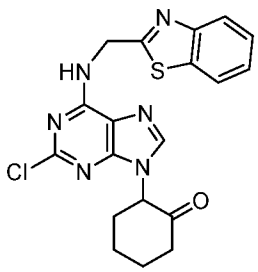
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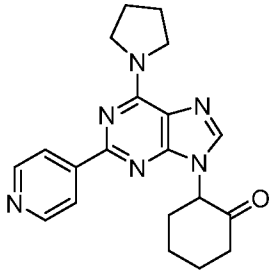
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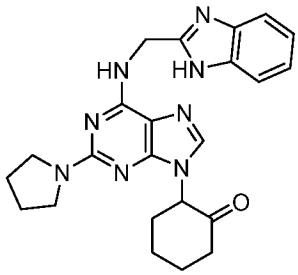
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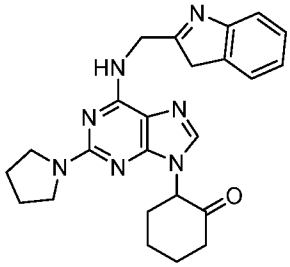
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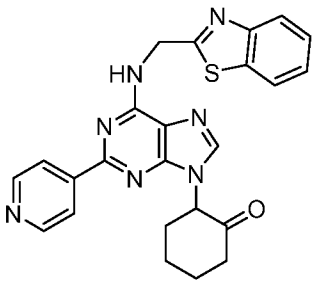
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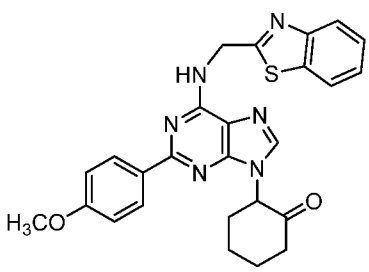
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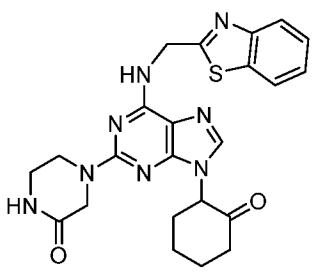
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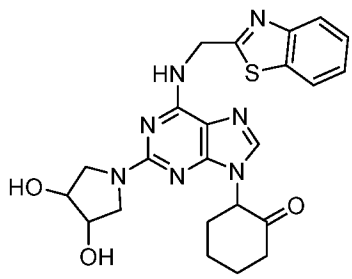
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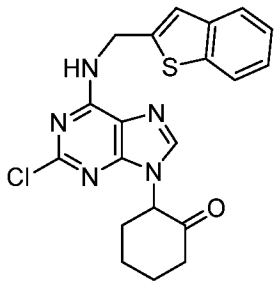
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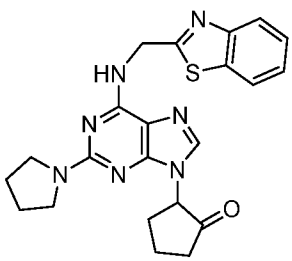
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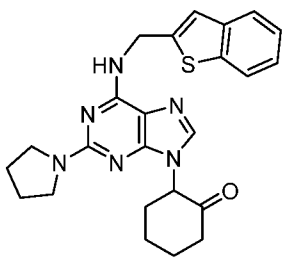
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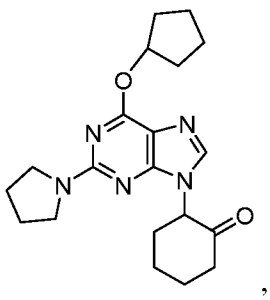
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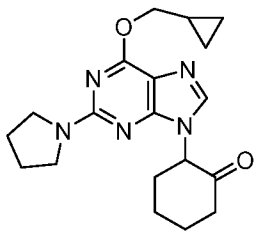
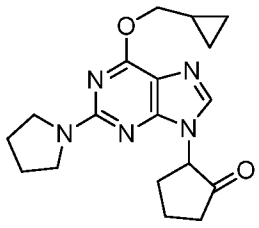
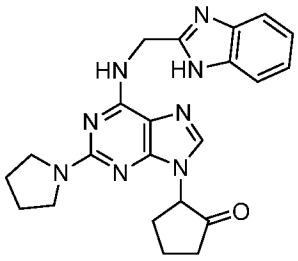
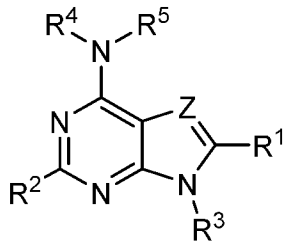

, 
, and 
,or a pharmaceutically acceptable salt thereof.

37. A compound of Formula (II):


(II)

or a pharmaceutically acceptable salt thereof, wherein:

Z is N or CH;

R^1 is H, C_1-C_6 alkyl, or C_1-C_6 heteroalkyl;

R^2 is C_1-C_6 heteroalkyl, $C(O)R^A$, $C(O)OR^B$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^A$, halo, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^6;

R^3 is H, C_1-C_6 alkyl, or C_1-C_6 heteroalkyl optionally substituted with 1-5 R^7;

R^4 is H, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8;

R^5 is H, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R^8;

or wherein R^4 and R^5 may be taken together to form a ring optionally substituted with 1-5 R^8;

each of R^6 and R^7 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, cyano, oxo, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein

each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-6 R^9;

R^8 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, OR^A, $C(O)R^B$, $C(O)OR^A$, $C(O)NR^CR^D$, NR^CR^D, $NR^CC(O)R^B$, $NR^CS(O)_pR^E$, $S(O)_pNR^CR^D$, $S(O)_pR^E$, halo, oxo, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9;

each of R^A, R^B, R^C, R^D, and R^E is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted optionally substituted with 1-5 R^9;

or wherein R^C and R^D are taken together with the nitrogen atom to which they are attached to form a heterocyclyl or heteroaryl ring, optionally substituted with 1-5 R^9;

R^9 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, hydroxyl, oxo, halo, cyano, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, or heterocyclyl is optionally substituted optionally substituted with 1-5 R^{10};

R^{10} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, halo, hydroxyl, or cycloalkyl;

R^{11} is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, halo, cyano, hydroxyl, or cycloalkyl; and

p is 0, 1, or 2.

38. The compound of claim 37, wherein Z is N.

39. The compound of claim 37, wherein Z is CH.

40. The compound of claim 37, wherein R^1 is H or C_1-C_6 alkyl (e.g., CH_3).

41. The compound of claim 37, wherein R^1 is H.

42. The compound claim 37, wherein R^2 is C_1-C_6 heteroalkyl, NR^CR^D, $NR^CC(O)R^B$, halo, cycloalkyl, or heterocyclyl.

43. The compound claim 37, wherein R^2 is NR^CR^D.

44. The compound claim 37, wherein R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl, heterocyclyl, aryl, or heteroaryl, optionally substituted with 1-5 R^9.

45. The compound claim 37, wherein R^2 is NR^CR^D and R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9.

46. The compound of claim 44, wherein R^C and R^D are each independently H, C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}.

47. The compound of claim 46, wherein R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), halo (e.g., fluoro), or hydroxyl.

48. The compound of claim 37, wherein R^2 is NR^CR^D, one of R^C and R^D is H and the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), optionally substituted with 1-5 R^9.

49. The compound of claim 48, wherein one of R^C and R^D is H, the other of R^C and R^D is C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, $CH_2CH_2CH_3$), or heterocyclyl (e.g., 5,6-dihydropyrimidinyl), and R^9, if present, is oxo or heterocyclyl (e.g., tetrahydrofuranyl), optionally substituted with 1-5 R^{10}.

50. The compound of claim 49, wherein R^{10} is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

51. The compound of claim 37, wherein R^2 is heterocyclyl optionally substituted with 1-5 R^6.

52. The compound of claim 37, wherein R^2 is a nitrogen-containing heterocyclyl, (e.g., a 6-membered nitrogen-containing heterocyclyl, e.g., piperazinyl, piperidinyl, morphilinyl), each of which is optionally substituted with 1-5 R^6 (e.g., $C(O)R^B$, oxo).

53. The compound of claim 52, wherein R^6 is $C(O)R^B$ or oxo, and R^B is C_1-C_6 heteroalkyl (e.g., methoxy).

54. The compound of claim 37, wherein R^2 is halo (e.g., chloro).

55. The compound of claim 37, wherein R^3 is H, C_1-C_6 alkyl (e.g., CH_2), or C_1-C_6 heteroalkyl (e.g., $CH_2CH_2OCH_3$ or CH_2CH_2N-) substituted with 0-2 R^7 (e.g., $(C(O)OCH_3)_2$).

56. The compound of claim 37, wherein R^3 is C_1-C_6 alkyl (e.g., CH_2) substituted with 1 R^7.

57. The compound of claim 37, wherein R^7 is heteroaryl.

58. The compound of claim 37, wherein R^7 is a bicyclic heteroaryl.

59. The compound of claim 37, wherein R^7 is a bicyclic heteroaryl (e.g., a nitrogen-containing bicyclic heteroaryl, e.g., benzothiazolyl, benzoxazole).

60. The compound of claim 37, wherein R^7 is benzothiazolyl (e.g., 2-benzothiazolyl) or benzoxazole (2-benzoxazole).

61. The compound of claim 37, wherein R^7 is benzothiazolyl (e.g., 2-benzothiazolyl).

62. The compound of claim 37, wherein R^4 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8.

63. The compound of claim 37, wherein R^4 is H.

64. The compound of claim 37, wherein R^5 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8.

65. The compound of claim 37, wherein R^5 is heterocyclyl (e.g., 5,6-dihydropyrimidinyl) optionally substituted with 1-5 R^8.

66. The compound of claim 65, wherein R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5 R^9.

67. The compound of claim 66, wherein R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

68. The compound of claim 37, wherein R^4 is H and R^5 is H, C_1-C_6 alkyl, cycloalkyl or heterocyclyl, each optionally substituted with 1-5 R^8.

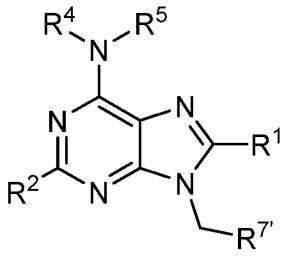
69. The compound of claim 68, wherein R^8 is oxo or heterocyclyl (e.g., tetrahydrofuranyl) optionally substituted with 1-5 R^9.

70. The compound of claim 69, wherein R^9 is C_1-C_6 heteroalkyl (e.g., methoxy), C_1-C_6 hydroxyalkyl (e.g., CH_2OH), halo (e.g., fluoro), or hydroxyl.

71. The compound of claim 37, wherein R^4 and R^5 are taken together to form a ring optionally substituted with 1-5 R^8.

72. The compound of claim 37, wherein R^4 and R^5 are taken together to form a heterocyclyl ring (e.g., pyrrolidinyl) optionally substituted with 1-5 R^8.

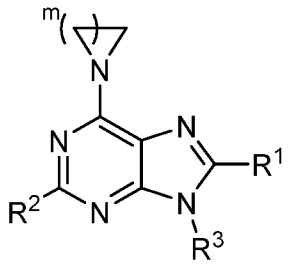
73. The compound of claim 37, wherein the compound is a compound of Formula (IIa):



(IIa),

or a pharmaceutically acceptable salt thereof, wherein each R^1, R^2, R^9, R^{10}, R^C, and R^D, are defined as for Formula (II), and $R^{7'}$ is heteroaryl.

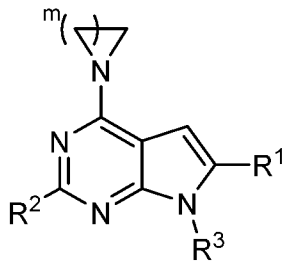
74. The compound of claim 37, wherein the compound is a compound of Formula (IIb):



(IIb)

or a pharmaceutically acceptable salt thereof, wherein each of R^2, R^3, R^9, R^{10}, R^C, and R^D are defined as for Formula (II), and m is 1, 2, 3, 4, or 5.

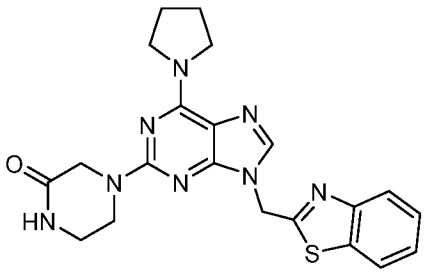
75. The compound of claim 37, wherein the compound is a compound of Formula (IIc):



(IIc)

or a pharmaceutically acceptable salt thereof, wherein each of R^2, R^3, R^9, R^{10}, R^C, and R^D are defined as for Formula (II), and m is 1, 2, 3, 4, or 5.

76. The compound of claim 37, wherein the compound is selected from:



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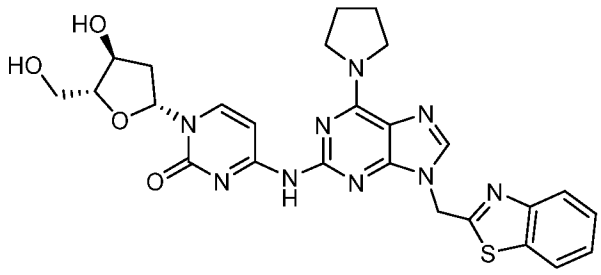

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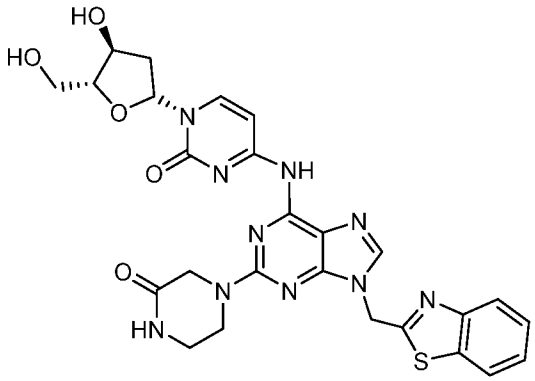

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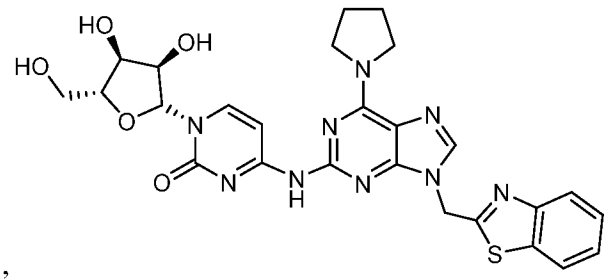

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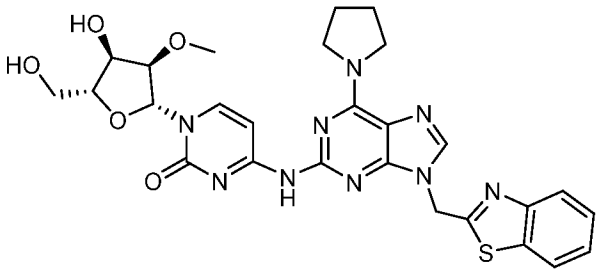

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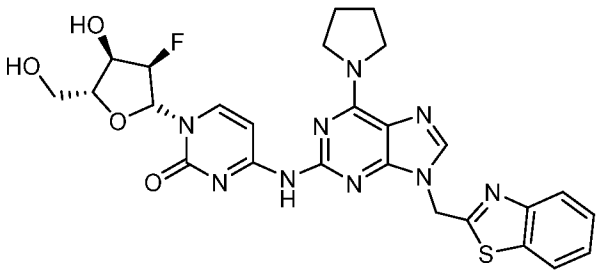

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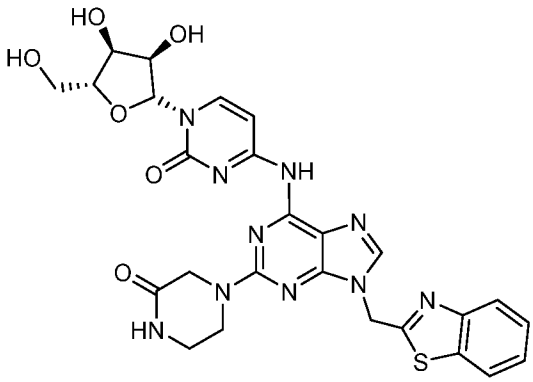

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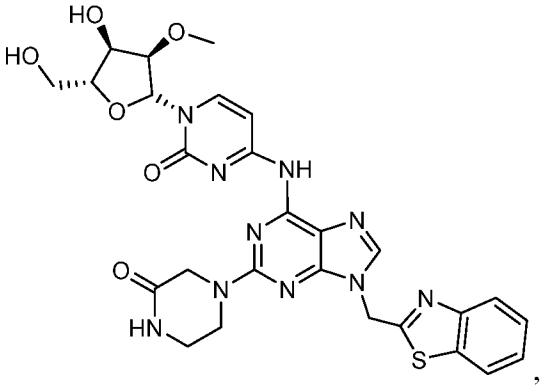
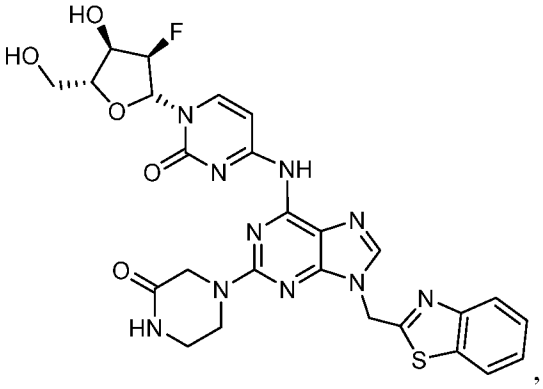
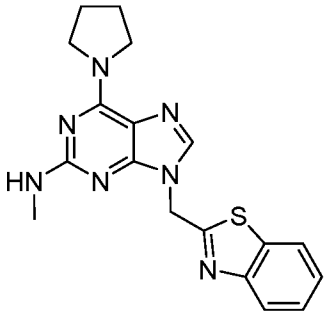
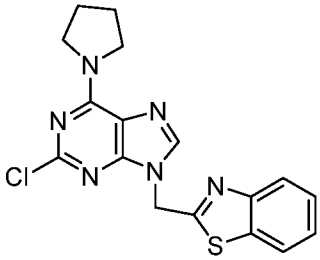
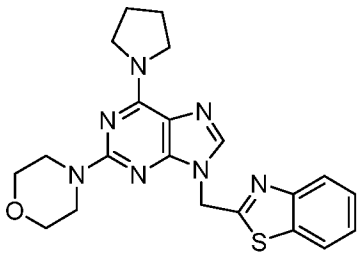
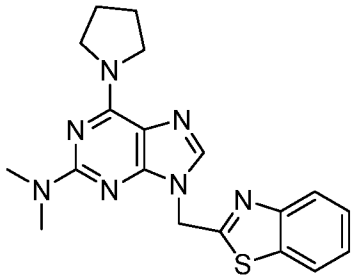


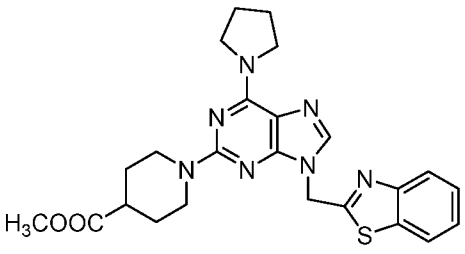


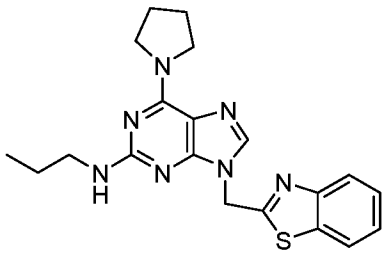


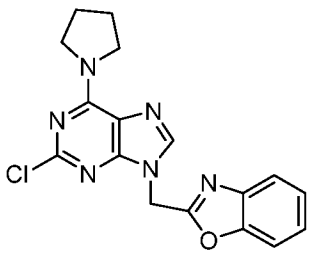


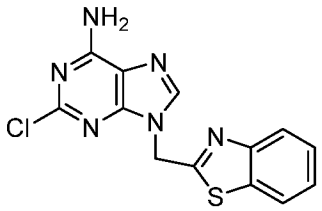


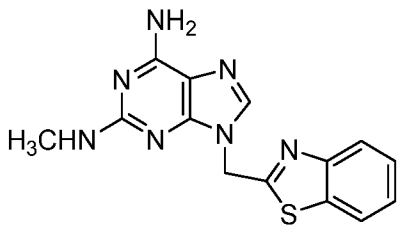


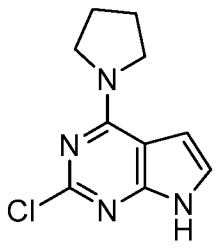


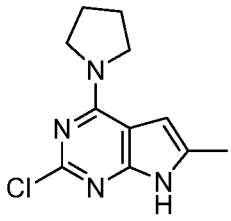


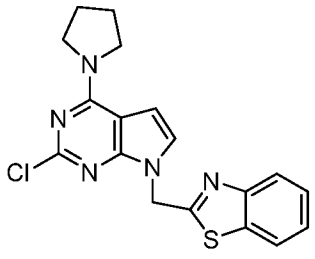
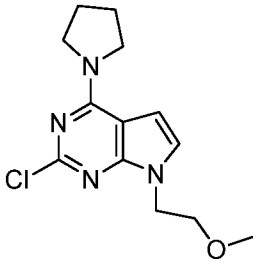
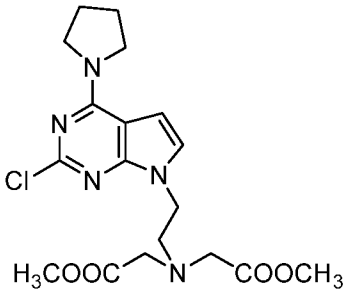










 ,  , and  , or a pharmaceutically acceptable salt thereof.

77. A pharmaceutical composition comprising a compound of any one of claims 1 or 37 and a pharmaceutically acceptable excipient or carrier.

78. A pharmaceutical composition comprising a compound of any one of claims 36 or 76 and a pharmaceutically acceptable excipient or carrier.

79. A method for inhibiting PDE4 activity in a cell or in a subject (e.g., PDE4B1 activity), comprising contacting the cell or administering to a subject an effective amount of a compound of any one of claims 1 or 37 or a pharmaceutical composition thereof.

80. A method for the treatment of an inflammatory disease or disorder comprising administering to a subject an effective amount of a compound of any one of claims 1 or 37 or a pharmaceutical composition thereof.

81. The method of claim 80, wherein the inflammatory disease or disorder comprises COPD, allergies, asthma, dermatitis, psoriasis, irritable bowel syndrome, ulcerative colitis.

82. A method for the treatment of a neurodegenerative disease or disorder comprising administering to a subject an effective amount of a compound of any one of claims 1 or 37 or a pharmaceutical composition thereof.

83. The method of claim 82, wherein the neurodegenerative disease or disorder comprises Alzheimer's disease, Huntington's disease, Parkinson's disease, dementia, amyotrophic lateral sclerosis, or motor neuron disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/13201

A. CLASSIFICATION OF SUBJECT MATTER
IPC - C07D 473/18, 473/20, 473/24 (2017.01)
CPC - C07D 473/18, 473/20, 473/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUBCHEM. CID 95121. 26 March 2005, pp. 1-15. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/95121>; page 3, formula	1-2, 19-21
X	PUBCHEM. CID 68455742. 30 November 2012, pp. 1-12. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/68455742>; page 4, formula	1, 3-4
X	PUBCHEM. CID 12918096. 08 February 2007, pp. 1-13. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/12918096>; page 4, formula	1, 5
X	PUBCHEM. CID 12777820. 08 February 2007, pp. 1-14. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/12777820>; page 3, formula	1, 11
X	PUBCHEM. CID 10060615. 25 October 2006, pp. 1-10. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/10060615>; page 3, formula	1, 13-15
X	PUBCHEM. CID 44475537. 07 December 2009, pp. 1-10. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/44475537>; page 3, formula	1, 17, 18
X	PUBCHEM. CID 10586466. 25 October 2006, pp. 1-13. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/10586466>; page 4, formula	1, 22-24

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2017 (19.04.2017)	19 MAY 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/13201

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Continued Within the Next Supplemental Box-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-36, 77-83

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/13201

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2008/0125446 A1 (KASIBHATLA, SR et al.) May 29, 2008; paragraphs [0011]-[0020], [0030], [0033]-[0034], [0043], [0053]-[0054], [0066], [0069], [0078]	1, 3-5, 9-28, 30, 77/1, 80/1 --- 2, 6-8, 31-36, 78/36, 81/80/1
Y	US 6,228,859 B1 (CAVALLA, DJ et al.) May 8, 2001; column 4, lines 28-65; column 5, line 9, 18-20; column 18, lines 8-19	2, 6-8, 31-34, 36, 78/36, 79/1, 81/80/1, 82/1, 83/82/1
Y	US 2008/0280926 A1 (PALLE, VP et al.) November 13, 2008; paragraphs [0009]-[0010], [0012], [0046]	1, 19, 29, 79/1, 82/1, 83/82/1
Y	US 6,319,928 B1 (CHASIN, M et al.) November 20, 2001; column 5, lines 1-11; column 6, lines 32-33; column 8, lines 50-51; column 9, lines 39-46	35
P, X	PUBCHEM. CID 117084947. 11 February 2007, pp. 1-10. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/117084947>; page 3, formula	1, 12

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US17/13201

Continuation of: Box III: Lack of Unity of Invention

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-36, 77 (in-part), 78 (in-part), 79 (in-part), 80 (in-part), 81 (in-part), 82 (in-part), and 83 (in-part) are directed toward a compound of Formula I wherein the core structure is a purine ring system wherein R3 is an optionally substituted cycloalkyl ring.

Group II: Claims 37-76, 77 (in-part), 78 (in-part), 79 (in-part), 80 (in-part), 81 (in-part), 82 (in-part), and 83 (in-part) are directed toward a compound of Formula II wherein the core structure is a purine ring system, or analog, wherein R3 is H, C1-C6 alkyl, or C1-C6 heteroalkyl optionally substituted with 1-5 R7.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include a purine ring system wherein R3 is an optionally substituted cycloalkyl ring, which is not present in Group II; and the special technical features of Group II include a purine ring system, or analog, wherein R3 is H, C1-C6 alkyl, or C1-C6 heteroalkyl optionally substituted with 1-5 R7, which is not present in Group II.

The common technical features of Groups I-II are a purine ring system, or analog, wherein R1 is H, C1-C6 alkyl, or C1-C6; R2 is C1-C6 heteroalkyl, C(O)RA, C(O)ORB, C(O)NRCRD, NRCRD, NRCC(O)RA, halo, cyano, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R6; RC and RD are independently H; R4 is H, C1-C6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R8; and R5 is H, C1-C6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-5 R8.

These common technical features are disclosed by the publication entitled "CID 68455742" to PubChem (hereinafter 'PubChem'742'). PubChem'742 discloses a purine ring system, or analog, wherein R1 is H; R2 is NRCRD; RC and RD are independently H; R4 is H; and R5 is H (compound, as shown; page 4).

Since the common technical features are previously disclosed by PubChem'742, these common features are not special and so Groups I-II lack unity.