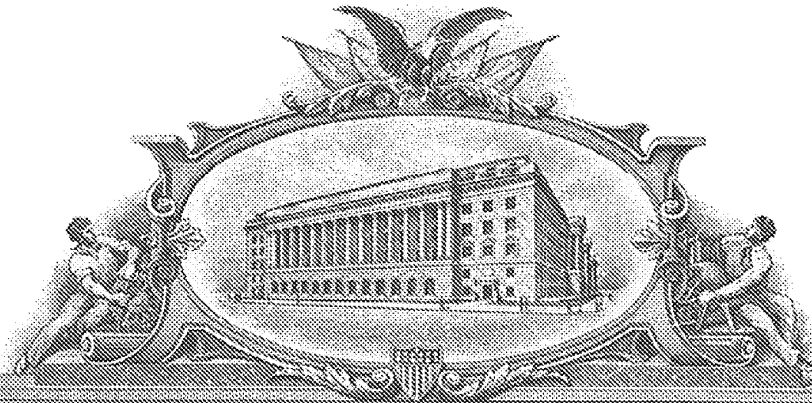


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Signature	/Frederick G. Vogt/			Date (YYYY-MM-DD)	2014-04-03
First Name	Frederick G.	Last Name	Vogt	Registration Number (If appropriate)	70115

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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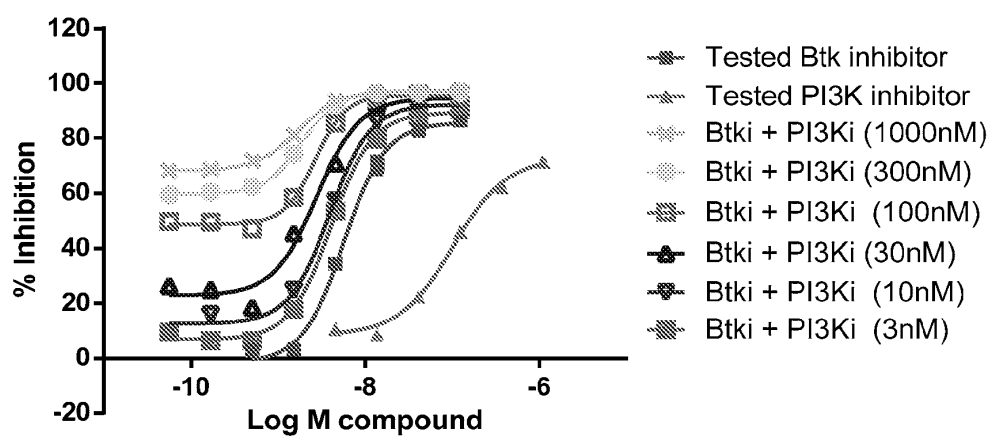


FIG. 1

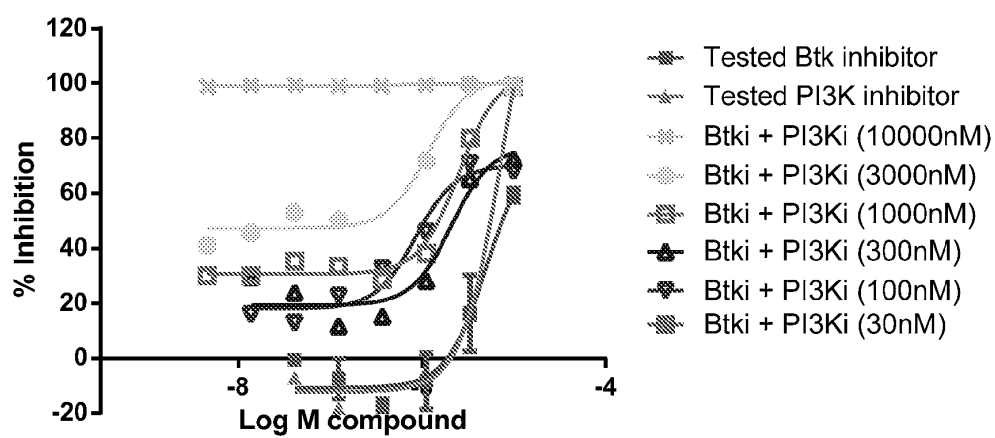


FIG. 2

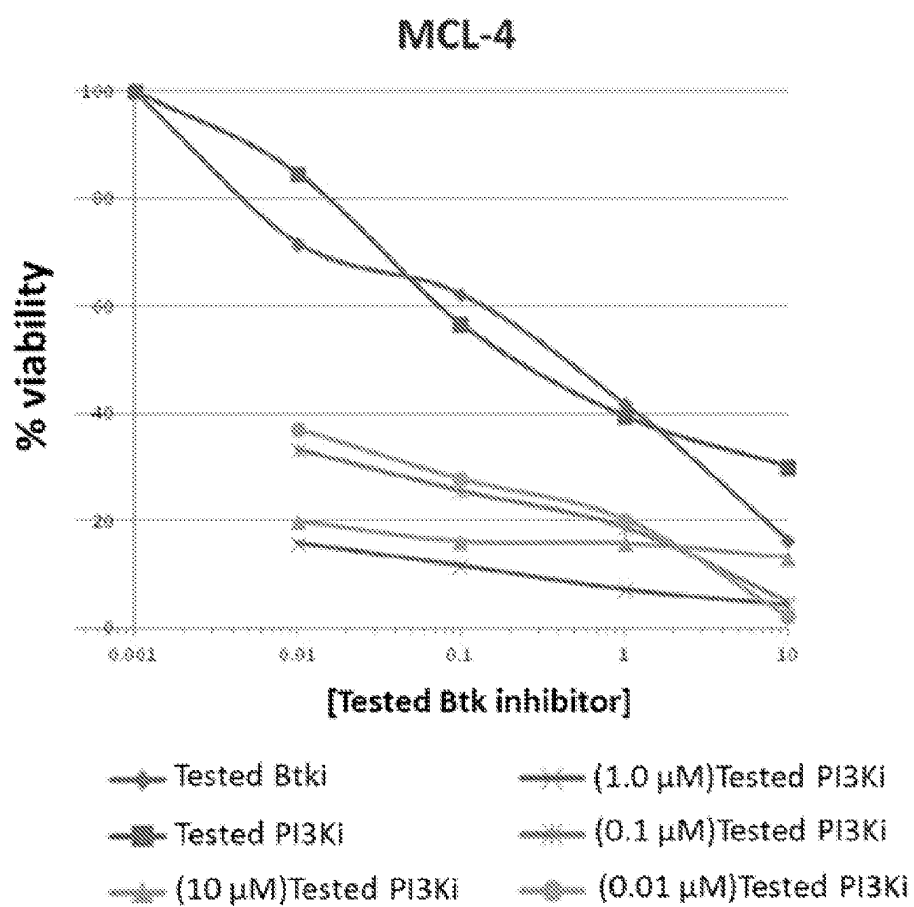


FIG. 3

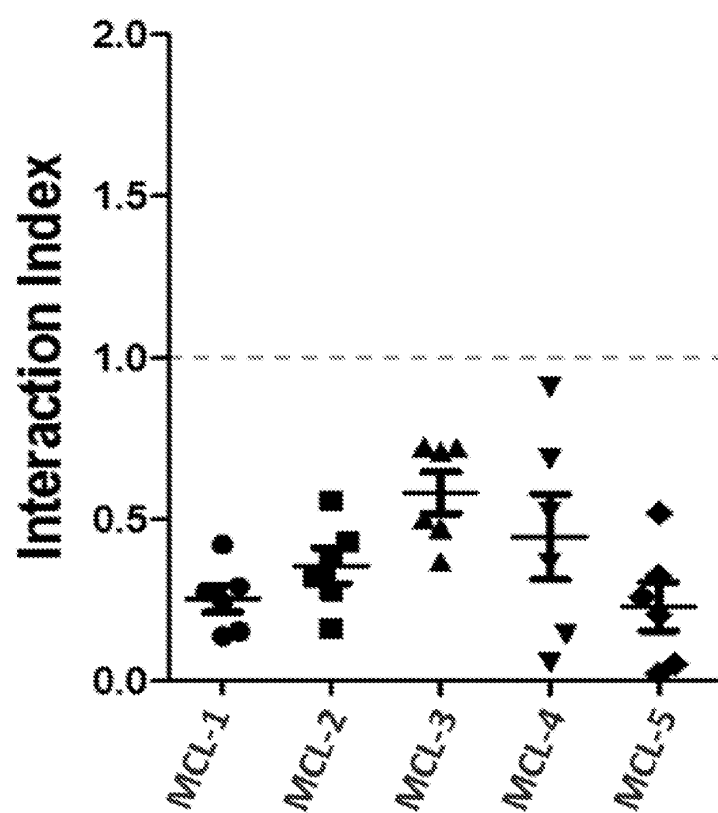


FIG. 4

Electronic Acknowledgement Receipt	
EFS ID:	18659888
Application Number:	61974665
International Application Number:	
Confirmation Number:	8182
Title of Invention:	Therapeutic Combination of a PI3K Inhibitor and a BTK Inhibitor
First Named Inventor/Applicant Name:	Ahmed Hamdy
Customer Number:	28977
Filer:	Frederick Vogt
Filer Authorized By:	
Attorney Docket Number:	055112-5002-PR1
Receipt Date:	03-APR-2014
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Application Type:	Provisional

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1	Provisional Cover Sheet (SB16)	20140403PROVTRANS.PDF	88450 0aa864b0f7237490a222b14da2ed7b029e1ef0ba	no	3
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THERAPEUTIC COMBINATION OF A PI3K INHIBITOR AND A BTK INHIBITOR

FIELD OF THE INVENTION

[001] A therapeutic combination of a phosphoinositide 3-kinase (PI3K) inhibitor and a Bruton's Tyrosine Kinase (BTK) inhibitor and uses of the therapeutic combination are disclosed herein.

BACKGROUND OF THE INVENTION

[002] PI3K inhibitors are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. PI3K inhibitors are key signaling enzymes that relay signals from cell surface receptors to downstream effectors. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3K inhibitors (p110 α , p110 β , p110 δ , and p110 γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases.

[003] The PI3K signaling pathway is known to be one of the most highly mutated in human cancers. PI3K signaling is also a key factor in disease states including hematologic malignancies, non-Hodgkin lymphoma (such as diffuse large B-cell lymphoma), allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome. The role of PI3K in cancer has been discussed, for example, in J. A. Engleman, *Nat. Rev. Cancer* **2009**, 9, 550-562. The PI3K- δ and PI3K- γ isoforms are preferentially expressed in normal and malignant leukocytes.

[004] The delta (δ) isoform of class I PI3K (PI3K- δ) is involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its role in immune system function, PI3K- δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis,

auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. The gamma (γ) isoform of class I PI3K (PI3K- γ) is also involved in immune system functions and plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

[005] Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family and has been implicated in a wide range of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been reported in various types of cancer.

[006] In view of the above, PI3K inhibitors are prime targets for drug development, as described in J. E. Kurt and I. Ray-Coquard, *Anticancer Res.* **2012**, 32, 2463-70. Several PI3K inhibitors are known, including those those that are PI3K- δ inhibitors, PI3K- γ inhibitors and those that are PI3K- δ,γ inhibitors.

[007] Bruton's Tyrosine Kinase (BTK) is a Tec family non-receptor protein kinase expressed in B cells and myeloid cells. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease characterized by a defect in B cell development with a block between pro- and pre-B cell stages. The result is an almost complete absence of B lymphocytes, causing a pronounced reduction of serum immunoglobulin of all classes. These findings support a key role for BTK in the regulation of the production of auto-antibodies in autoimmune diseases.

[008] Other diseases with an important role for dysfunctional B cells are B cell malignancies. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies, as described in O. Cruz et al., *OncoTargets and Therapy* **2013**, 6, 161-176.

[009] The present invention includes the unexpected discovery that the combination of a PI3K inhibitor with a BTK inhibitor is effective in the treatment of any of several types of cancers such as leukemia, lymphoma and solid tumor cancers.

SUMMARY OF THE INVENTION

[0010] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K inhibitor and a BTK inhibitor.

[0011] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K- γ inhibitor and a BTK inhibitor.

[0012] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K- δ inhibitor and a BTK inhibitor.

[0013] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K- γ,δ inhibitor and a BTK inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[0015] FIG. 1 illustrates the sensitivity of the TMD8 diffuse large B cell lymphoma (DLBCL) cell line to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[0016] FIG. 2 illustrates the sensitivity of the MINO mantle cell lymphoma cell to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[0017] FIG. 3 illustrates the proproliferative activity in primary mantle cell lymphoma cells of Formula XVIII ("Tested Btki") and Formula IX ("Tested PI3Ki"). The percentage viability of cells ("% viability", y-axis) is plotted versus the concentration of the Formula XVIII ("Tested Btk Inhibitor", x-axis). The concentration of the individual BTK and PI3K inhibitors (i.e. not in combination) are also given on the x-axis.

[0018] FIG. 4 illustrates the interaction index of the combination of the BTK inhibitor of Formula XVIII and the PI3K inhibitor of Formula IX in primary mantle cell lymphoma cells.

DETAILED DESCRIPTION OF THE INVENTION

[0019] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[0021] The terms "co-administration" and "administered in combination with" as used herein, encompass administration of two or more agents to a subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0022] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, *etc.* which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0023] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0024] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and

basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In selected embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0025] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

[0026] "Prodrug" is intended to describe a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers the advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgaard, H., Design of Prodrugs (1985) (Elsevier, Amsterdam). The term "prodrug" is also intended to include any covalently bonded carriers, which release the active compound *in vivo* when administered to a subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to yield the active parent compound. Prodrugs include, for example, compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetates, formates and benzoate derivatives of an alcohol, various ester derivatives of a carboxylic acid, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound.

[0027] The term "*in vivo*" refers to an event that takes place in a subject's body.

[0028] The term "*in vitro*" refers to an event that takes places outside of a subject's body. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

[0029] Unless otherwise stated, the chemical structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds where one or more hydrogen atoms is replaced by deuterium or tritium, or wherein one or more carbon atoms is replaced by ¹³C- or ¹⁴C-enriched carbons, are within the scope of this invention.

[0030] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that "consist of" or "consist essentially of" the described features.

[0031] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C₁-C₁₀ alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl and decyl. The alkyl moiety may be attached to the rest of the molecule by a single bond, such as for example, methyl (Me), ethyl (Et), n-propyl (Pr), 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is

optionally substituted by one or more of substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂ where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0032] "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0033] "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0034] "Alkylheterocycloalkyl" refers to an -(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

[0035] An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0036] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, C₂-C₁₀ alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkenyl moiety may be attached to the rest of the molecule by a single bond, such as for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl and penta-1,4-dienyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally

substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0037] "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

[0038] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e. C₂-C₁₀ alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - e.g., "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0039] "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

[0040] "Carboxaldehyde" refers to a $-(C=O)H$ radical.

[0041] "Carboxyl" refers to a $-(C=O)OH$ radical.

[0042] "Cyano" refers to a $-CN$ radical.

[0043] "Cycloalkyl" refers to a monocyclic or polycyclic 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_2 - C_{10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - *e.g.*, "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0044] "Cycloalkyl-alkenyl" refers to a $-(cycloalkyl)alkenyl$ radical where cycloalkyl and alkenyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkenyl, respectively.

[0045] "Cycloalkyl-heterocycloalkyl" refers to a $-(cycloalkyl)heterocycloalkyl$ radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heterocycloalkyl, respectively.

[0046] "Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heteroaryl, respectively.

[0047] The term "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy and cyclohexyloxy. "Lower alkoxy" refers to alkoxy groups containing one to six carbons.

[0048] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (*i.e.*, -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0049] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C₁-C₆ alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group.

[0050] The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,

hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0051] "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)- and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the alkyl, aryl or heteroaryl moiety of the acyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0052] "Acyloxy" refers to a R(C=O)O- radical wherein "R" is alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl, which are as described herein. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is

independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0053] "Amino" or "aminc" refers to a $-N(R^a)_2$ radical group, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a $-N(R^a)_2$ group has two R^a substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, $-N(R^a)_2$ is intended to include, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0054] The term "substituted amino" also refers to N-oxides of the groups $-NHR^d$, and NR^dR^d each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid.

[0055] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R)_2$ or $-NHC(O)R$, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The R_2 of $-N(R)_2$ of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound of Formula (I), thereby forming a prodrug. The procedures and specific groups to make such amides are known to those of skill in the art and

can readily be found in seminal sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

[0056] "Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms (*e.g.*, C₆-C₁₀ aromatic or C₆-C₁₀ aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group may consist of 6 ring atoms, 7 ring atoms, *etc.*, up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0057] "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl-radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0058] "Ester" refers to a chemical radical of formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The procedures and specific groups to make

esters are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0059] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

[0060] "Halo", "halide", or, alternatively, "halogen" is intended to mean fluoro, chloro, bromo or iodo. The terms "haloalkyl", "haloalkenyl", "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl 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.

[0061] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have 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., C₁-C₄ heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -

$N(R^a)_tS(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0062] "Heteroalkylaryl" refers to an $-(\text{heteroalkyl})\text{aryl}$ radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl, respectively.

[0063] "Heteroalkylheteroaryl" refers to an $-(\text{heteroalkyl})\text{heteroaryl}$ radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl, respectively.

[0064] "Heteroalkylheterocycloalkyl" refers to an $-(\text{heteroalkyl})\text{heterocycloalkyl}$ radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl, respectively.

[0065] "Heteroalkylcycloalkyl" refers to an $-(\text{heteroalkyl})\text{cycloalkyl}$ radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl, respectively.

[0066] "Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (*e.g.*, C_5 - C_{13} heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range - *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical - *e.g.*, a pyridyl group with two points of attachment is a pyridylidene. A N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical are

optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl(benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thio, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen,

alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0067] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl N-oxides.

[0068] "Heteroarylalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

[0069] "Heterocycloalkyl" refers 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 and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range - *e.g.*, "3 to 18 ring atoms" means that the heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, *etc.*, up to and including 18 ring atoms. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolynyl, imidazolidynyl, isothiazolidynyl, isoxazolidynyl, morpholynyl, octahydroindolyl, octahydroisindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidynyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidynyl, quinuclidynyl, thiazolidynyl, tetrahydrofuryl, trithianyl, tetrahydropyranlyl, thiomorpholynyl, thiamorpholynyl, 1-oxo-thiomorpholynyl, and 1,1-dioxo-thiomorpholynyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen,

alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0070] "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

[0071] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - *i.e.*, having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0072] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For

example, if a compound, which may potentially have an (R)- or an (S)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (R)- or (S)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (S)- and 20% (R)-, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or the Pirkle alcohol, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[0073] "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0074] "Nitro" refers to the -NO₂ radical.

[0075] "Oxa" refers to the -O- radical.

[0076] "Oxo" refers to the =O radical.

[0077] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[0078] The terms "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (R)-enantiomer, such as at least 75% by weight, such as at least 80% by weight. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, such as at least 90% by weight, such as at least 95% by weight.

[0079] In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers 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 enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); and E. L. Eliel, Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962).

[0080] A "leaving group or atom" is any group or atom that will, under selected reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Examples of such groups, unless otherwise specified, include halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[0081] "Protecting group" is intended to mean a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and the group can then be readily removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999).

[0082] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[0083] "Substituted" means that the referenced group may have attached one or more additional moieties individually and independently selected from, for example, acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and protected derivatives thereof. The substituents themselves may be substituted, for example, a cycloalkyl substituent may itself have a halide substituent at one or more of its ring carbons.

[0084] "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

[0085] "Sulfinyl" refers to groups that include -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl) and -S(O)-(optionally substituted heterocycloalkyl).

[0086] "Sulfonyl" refers to groups that include -S(O₂)-H, -S(O₂)-(optionally substituted alkyl), -S(O₂)-(optionally substituted amino), -S(O₂)-(optionally substituted aryl), -S(O₂)-(optionally substituted heteroaryl), and -S(O₂)-(optionally substituted heterocycloalkyl).

[0087] "Sulfonamidyl" or "sulfonamido" refers to a -S(=O)₂-NRR radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in -NRR of the -S(=O)₂-NRR radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[0088] "Sulfoxyl" refers to a -S(=O)₂OH radical.

[0089] "Sulfonate" refers to a $-S(=O)_2-OR$ radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[0090] Compounds of the invention also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" are intended to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to.

Co-administration of compounds

[0091] An aspect of the invention is a composition, such as a pharmaceutical composition, comprising a combination of a PI3K inhibitor and a BTK inhibitor.

[0092] Another aspect of the invention is a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination of a PI3K inhibitor and a BTK inhibitor.

[0093] In an exemplary embodiment, the PI3K inhibitor is a PI3K- γ inhibitor.

[0094] In an exemplary embodiment, the PI3K inhibitor is a PI3K- δ inhibitor.

[0095] In an exemplary embodiment, the PI3K inhibitor is a PI3K- γ,δ inhibitor.

[0096] In an exemplary embodiment, the PI3K inhibitor is a selective PI3K inhibitor.

[0097] In an exemplary embodiment, the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers.

[0098] In an exemplary embodiment, the leukemia is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL).

[0099] In an exemplary embodiment, the combination of the the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor with the BTK inhibitor is administered by intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

[00100] In an exemplary embodiment, the the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is in the form of a pharmaceutically acceptable salt.

[00101] In an exemplary embodiment, the BTK inhibitor is in the form of a pharmaceutically acceptable salt.

[00102] In an exemplary embodiment, the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is administered to the subject before administration of the BTK inhibitor.

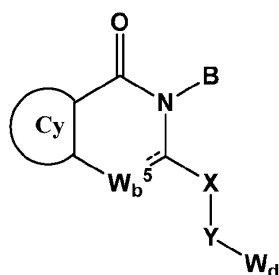
[00103] In an exemplary embodiment, the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is administered concurrently with the administration of the BTK inhibitor.

[00104] In an exemplary embodiment, the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, PI3K- γ,δ inhibitor is administered to the subject after administration of the BTK inhibitor.

[00105] In an exemplary embodiment, the subject is a mammal, such as a human.

PI3K Inhibitors

[00106] In an exemplary embodiment, the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 8,193,182 and 8,569,323, and U.S. Patent Application Publication Nos. 2012/0184568 A1, 2013/0344061 A1, and 2013/0267521 A1, the disclosures of which are incorporated by reference herein. In an exemplary embodiment, the the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

Cy is aryl or heteroaryl substituted by 0 or 1 occurrences of R^3 and 0, 1, 2, or 3 occurrences of R^5 ;

W_b^5 is CR^8 , CHR^8 , or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, 3, or 4 occurrences of R^2 ;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, or carbonate;

X is $-(CH(R^9))_z-$;

Y is $-N(R^9)-C(=O)-$, $-C(=O)-N(R^9)-$, $-C(=O)-N(R^9)-(CHR^9)-$, $-N(R^9)-S(=O)-$, $-S(=O)-N(R^9)-$, $S(=O)_2-N(R^9)-$, $-N(R^9)-C(=O)-N(R^9)$ or $-N(R^9)S(=O)_2-$;

z is an integer of 1, 2, 3, or 4;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro;

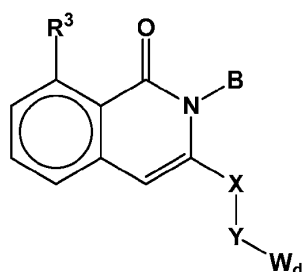
each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or heteroalkyl; or two adjacent occurrences of R^9 together with the atoms to which they are attached form a 4- to 7-membered ring;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl, each of which is substituted with one or more R^{10} , R^{11} , R^{12} or R^{13} , and

R^{10} , R^{11} , R^{12} and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate or $NR'R''$ wherein R' and R'' are taken together with nitrogen to form a cyclic moiety.

[00107] In an exemplary embodiment, the the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is a compound of Formula (I-1):

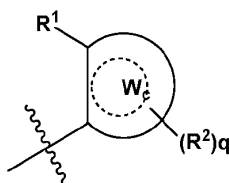


Formula (I-1)

or a pharmaceutically acceptable salt thereof,

wherein:

B is a moiety of Formula (II):



Formula (II) ;

W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

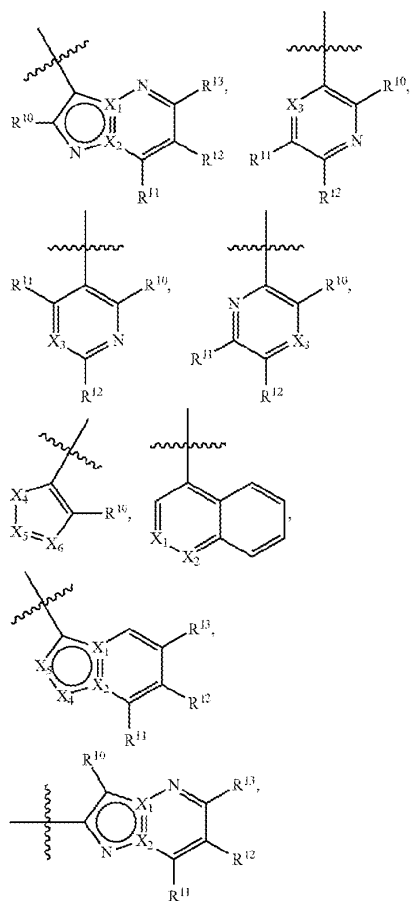
q is an integer of 0, 1, 2, 3, or 4;

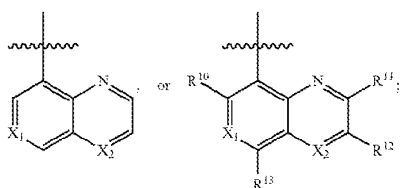
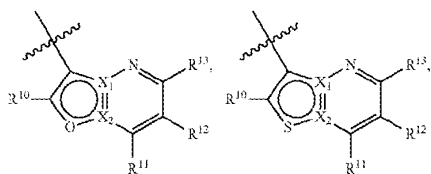
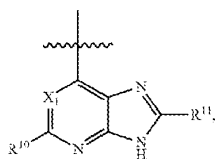
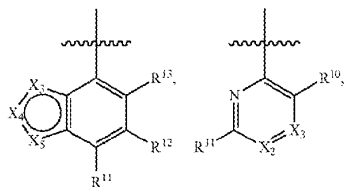
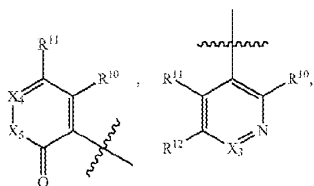
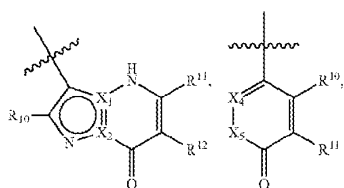
X is a bond or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3 or 4;

Y is a bond, $-N(R^9)-$, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)(CHR^9)_z-$, $-N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$ or $-N(R^9)C(R^9)_2-$;

z is an integer of 1, 2, 3, or 4;

W_d is:



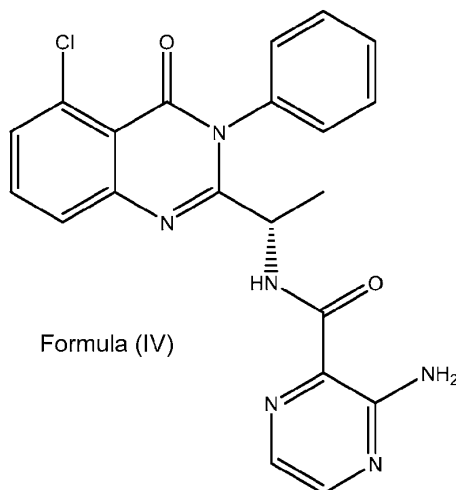
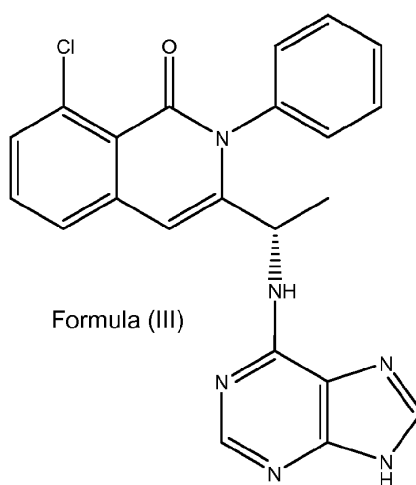


X_1 , X_2 and X_3 are each independently C, CR¹³ or N; and X_4 , X_5 and X_6 are each independently N, NH, CR¹³, S or O;

R¹ is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; $R_{sup.3}$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy or nitro; and each instance of R^9 is independently hydrogen, alkyl, or heterocycloalkyl.

[00108] In an exemplary embodiment, the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is a compound of Formula (III) or Formula (IV):

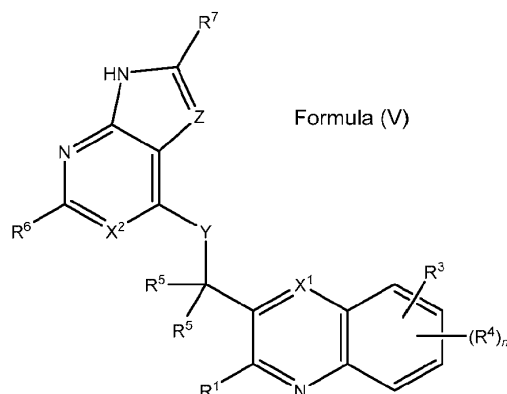


or a pharmaceutically acceptable salt thereof.

[00109] In an exemplary embodiment, the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one or a pharmaceutically acceptable salt thereof.

[00110] In an exemplary embodiment, the PI3K inhibitor, PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor is (S)-3-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide or a pharmaceutically acceptable salt thereof.

[00111] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 8,193,199 and 8,586,739, the disclosure of which is incorporated by reference herein. In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (V):



or any pharmaceutically-acceptable salt thereof, wherein:

X¹ is C(R⁹) or N;

X² is C(R₁₀) or N;

Y is N(R¹¹), O or S;

Z is CR⁸ or N;

n is 0, 1, 2 or 3;

R¹ is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are

substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl;

R² is selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, OS(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a and —NR^aC₂₋₆alkylOR^a; or R² is selected from C₁₋₆alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C₁₋₃alkyl)heteroaryl, —(C₁₋₃alkyl)heterocycle, —O(C₁₋₃alkyl)heteroaryl, —O(C₁₋₃alkyl)heterocycle, —NR^a(C₁₋₃alkyl)heteroaryl, —NR^a(C₁₋₃alkyl)heterocycle, —(C₁₋₃alkyl)phenyl, —O(C₁₋₃alkyl)phenyl and —NR^a(C₁₋₃alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄haloalkyl, OC₁₋₄alkyl, Br, Cl, F, I and C₁₋₄alkyl;

R³ is selected from H, halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)R^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R², —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aNR^aR^a, —NR^aC₂₋₆alkylOR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl;

R⁴ is, independently, in each instance, halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl or C₁₋₄haloalkyl;

R⁵ is, independently, in each instance, H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, or C₁₋₆alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl; or both R⁵ groups together form a C₃₋₆spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl;

R^6 is selected from H, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$;

R^7 is selected from H, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$;

R^8 is selected from H, C_{1-6} haloalkyl, Br, Cl, F, I, OR^a , NR^aR^a , C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} haloalkyl, OC_{1-6} alkyl, Br, Cl, F, I and C_{1-6} alkyl;

R^9 is selected from H, halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^aC(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, NR^aR^a , $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{1-6}alkyl$, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, NR^aR^a , $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$,

$S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

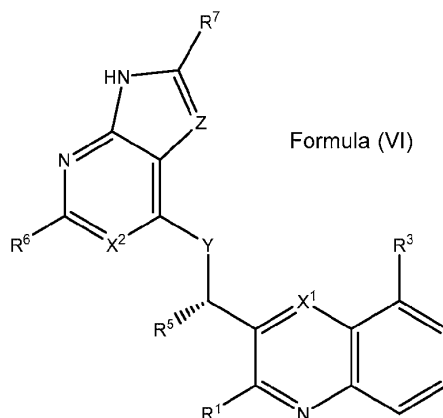
R^{10} is H, $C_{1-3}alkyl$, $C_{1-3}haloalkyl$, cyano, nitro, CO_2R^a , $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

R^{11} is H or $C_{1-4}alkyl$;

R^a is independently, at each instance, H or R^b ; and

R^b is independently, at each instance, phenyl, benzyl or $C_{1-6}alkyl$, the phenyl, benzyl and $C_{1-6}alkyl$ being substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}alkyl$, $C_{1-3}haloalkyl$, $-OC_{1-4}alkyl$, $-NH_2$, $-NHC_{1-4}alkyl$, $-N(C_{1-4}alkyl)C_{1-4}alkyl$.

[00112] In another exemplary embodiment, the the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (VI):



or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R¹ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl;

R² is selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a and —NR^aC₂₋₆alkylOR^a; or R² is selected from C₁₋₆alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C₁₋₃alkyl)heteroaryl, —(C₁₋₃alkyl)heterocycle, —O(C₁₋₃alkyl)heteroaryl, —O(C₁₋₃alkyl)heterocycle, —NR^a(C₁₋₃alkyl)heteroaryl, —NR^a(C₁₋₃alkyl)heterocycle, —(C₁₋₃alkyl)phenyl, —O(C₁₋₃alkyl)phenyl and —NR^a(C₁₋₃alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄haloalkyl, OC₁₋₄alkyl, Br, Cl, F, I and C₁₋₄alkyl;

R³ is selected from H, halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, C(=O)NR^aR^aC(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylOR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl;

R⁴ is, independently, in each instance, halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl or C₁₋₄haloalkyl;

R⁵ is, independently, in each instance, H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, or C₁₋₆alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl,

OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl; or both R⁵ groups together form a C₃₋₆-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl;

R⁶ is selected from H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a;

R⁷ is selected from H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^aS(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a;

R⁸ is selected from H, C₁₋₆haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl;

R⁹ is selected from H, halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a, —NR^aC₂₋₆alkylOR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^a, —NR^aC₂₋₆alkylOR^a; or R⁹ is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1,

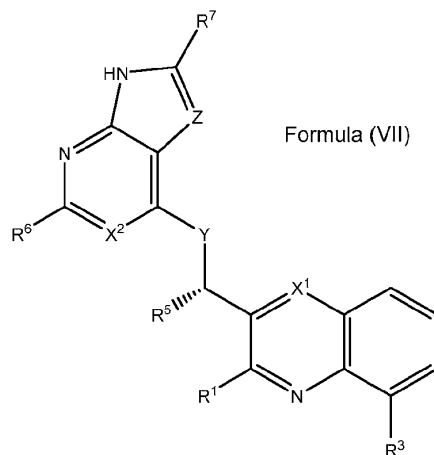
2, 3 or 4 substituents selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a and —NR^aC₂₋₆alkylOR^a;

R¹⁰ is H, C₁₋₃alkyl, C₁₋₃haloalkyl, cyano, nitro, CO₂R^a, C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —S(=O)R^b, S(=O)₂R^b or S(=O)₂NR^aR^a; —R¹¹ is H or C₁₋₄alkyl;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C₁₋₆alkyl, the phenyl, benzyl and C₁₋₆alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C₁₋₄alkyl, C₁₋₃haloalkyl, —OC₁₋₄alkyl, —NH₂, —NHC₁₋₄alkyl, —N(C₁₋₄alkyl)C₁₋₄alkyl.

[00113] In another exemplary embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VII):



or any pharmaceutically-acceptable salt thereof, wherein:

X¹ is C(R⁹) or N;

X² is C(R¹⁰) or N;

Y is N(R¹¹), O or S;

Z is CR⁸ or N;

n is 0, 1, 2 or 3;

R¹ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl;

R² is selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a and —NR^aC₂₋₆alkylOR^a; or R² is selected from C₁₋₆alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C₁₋₃alkyl)heteroaryl, —(C₁₋₃alkyl)heterocycle, —O(C₁₋₃alkyl)heteroaryl, —O(C₁₋₃alkyl)heterocycle, —NR^a(C₁₋₃alkyl)heteroaryl, —NR^a(C₁₋₃alkyl)heterocycle, —(C₁₋₃alkyl)phenyl, —O(C₁₋₃alkyl)phenyl and —NR^a(C₁₋₃alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄haloalkyl, OC₁₋₄alkyl, Br, Cl, F, I and C₁₋₄alkyl;

R³ is selected from H, halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR¹, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a, —NR^aC₂₋₆alkylOR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl;

R⁴ is, independently, in each instance, halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl or C₁₋₄haloalkyl;

R⁵ is, independently, in each instance, H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, or C₁₋₆alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl; or both R⁵ groups together form a C₃₋₆-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl;

R⁶ is selected from H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^aS(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a;

R⁷ is selected from H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^aS(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a;

R⁸ is selected from H, C₁₋₆haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl;

R⁹ is selected from H, halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylOR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR⁸, —OC(=O)R⁸, —OC(=O)NR²R⁸, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R⁸, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —

$\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$, $\text{—NR}^a\text{C}_{2-6}\text{alkylOR}^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $\text{C}_{1-4}\text{haloalkyl}$, cyano, nitro, —C(=O)R^a , —C(=O)OR^a , $\text{—C(=O)NR}^a\text{R}^a$, $\text{—C(=NR}^a\text{)NR}^a\text{R}^a$, —OR^a , —OC(=O)R^a , $\text{—OC(=O)NR}^a\text{R}^a$, $\text{—OC(=O)N(R}^a\text{)S(=O)}_2\text{R}^a$, $\text{—OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $\text{—OC}_{2-6}\text{alkylOR}^a$, —SR^a , —S(=O)R^a , $\text{—S(=O)}_2\text{R}^a$, $\text{—S(=O)}_2\text{NR}^a\text{R}^a$, $\text{—S(=O)}_2\text{N(R}^a\text{)C(=O)R}^a$, $\text{—S(=O)}_2\text{N(R}^a\text{)C(=O)OR}^a$, $\text{—S(=O)}_2\text{N(R}^a\text{)C(=O)NR}^a\text{R}^a$, $\text{—NR}^a\text{R}^a$, $\text{—N(R}^a\text{)C(=O)R}^a$, $\text{—N(R}^a\text{)C(=O)OR}^a$, $\text{—N(R}^a\text{)C(=O)NR}^a\text{R}^a$, $\text{—N(R}^a\text{)C(=NR}^a\text{)NR}^a\text{R}^a$, $\text{—N(R}^a\text{)S(=O)}_2\text{R}^a$, $\text{—N(R}^a\text{)S(=O)}_2\text{NR}^a\text{R}^a$, $\text{—NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $\text{—NR}^a\text{C}_{2-6}\text{alkylOR}^a$;

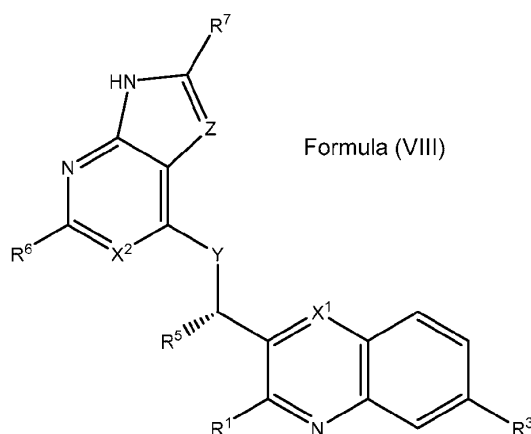
R^{10} is H, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{haloalkyl}$, cyano, nitro, CO_2R^a , $\text{C(=O)NR}^a\text{R}^a$, $\text{—C(=NR}^a\text{)NR}^a\text{R}^a$, $\text{—S(=O)}_2\text{N(R}^a\text{)C(=O)R}^a$, $\text{—S(=O)}_2\text{N(R}^a\text{)C(=O)OR}^a$, $\text{—S(=O)}_2\text{N(R}^a\text{)C(=O)NR}^a\text{R}^a$, —S(=O)R^b , $\text{S(=O)}_2\text{R}^b$ or $\text{S(=O)}_2\text{NR}^a\text{R}^a$;

R^{11} is H or $\text{C}_{1-4}\text{alkyl}$;

R^a is independently, at each instance, H or R^b ; and

R^b is independently, at each instance, phenyl, benzyl or $\text{C}_{1-6}\text{alkyl}$, the phenyl, benzyl and $\text{C}_{1-6}\text{alkyl}$ being substituted by 0, 1, 2 or 3 substituents selected from halo, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-3}\text{haloalkyl}$, $\text{—OC}_{1-4}\text{alkyl}$, —NH_2 , $\text{—NHC}_{1-4}\text{alkyl}$, $\text{—N(C}_{1-4}\text{alkyl)C}_{1-4}\text{alkyl}$.

[00114] In another exemplary embodiment, the the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (VIII):



Formula (VIII)

or any pharmaceutically-acceptable salt thereof, wherein:

X¹ is C(R⁹) or N;

X² is C(R¹⁰) or N;

Y is N(R¹¹), O or S;

Z is CR⁸ or N;

n is 0, 1, 2 or 3;

R¹ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl;

R² is selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a and —NR^aC₂₋₆alkylOR^a; or R² is selected from C₁₋₆alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C₁₋₃alkyl)heteroaryl, —(C₁₋₃alkyl)heterocycle, —O(C₁₋₃alkyl)heteroaryl, —O(C₁₋₃alkyl)heterocycle, —NR^a(C₁₋₃alkyl)heteroaryl, —NR^a(C₁₋₃alkyl)heterocycle, —(C₁₋₃alkyl)phenyl, —O(C₁₋₃alkyl)phenyl and —NR^a(C₁₋₃alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C₁₋₄haloalkyl, OC₁₋₄alkyl, Br, Cl, F, I and C₁₋₄alkyl;

R³ is selected from H, halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —

NR^a, —NR^aC₂₋₆alkylOR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl;

R⁴ is, independently, in each instance, halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl or C₁₋₄haloalkyl;

R⁵ is, independently, in each instance, H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, or C₁₋₆alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl; or both R⁵ groups together form a C₃₋₆-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl;

R⁶ is selected from H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a;

R⁷ is selected from H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a;

R⁸ is selected from H, C₁₋₆haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl;

R⁹ is selected from H, halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)₂NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(=O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a, —NR^aC₂₋₆alkylOR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —

$\text{S(=O)}_2\text{R}^a$, $-\text{S(=O)}_2\text{NR}^a\text{R}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)R}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)OR}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N(R}^a\text{)C(=O)R}^a$, $-\text{N(R}^a\text{)C(=O)OR}^a$, $-\text{N(R}^a\text{)C(=O)NR}^a\text{R}^a$, $-\text{N(R}^a\text{)C(=NR}^a\text{)NR}^a\text{R}^a$, $-\text{N(R}^a\text{)S(=O)}_2\text{R}^a$, $-\text{N(R}^a\text{)S(=O)}_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $\text{C}_{1-4}\text{haloalkyl}$, cyano, nitro, $-\text{C(O)R}^a$, $-\text{C(=O)OR}^a$, $-\text{C(=O)NR}^a\text{R}^a$, $-\text{C(=NR}^a\text{)NR}^a\text{R}^a$, $-\text{OR}^a$, $-\text{OC(=O)R}^a$, $-\text{OC(=O)NR}^a\text{R}^a$, $-\text{OC(=O)N(R}^a\text{)S(=O)}_2\text{R}^a$, $-\text{OC}_{2-6}\text{alkylNR}^a\text{R}^a$, $-\text{OC}_{2-6}\text{alkylOR}^a$, $-\text{SR}^a$, $-\text{S(=O)R}^a$, $-\text{S(=O)}_2\text{R}^a$, $-\text{S(=O)}_2\text{NR}^a\text{R}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)R}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)OR}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)NR}^a\text{R}^a$, $-\text{NR}^a\text{R}^a$, $-\text{N(R}^a\text{)C(=O)R}^a$, $-\text{N(R}^a\text{)C(=O)OR}^a$, $-\text{N(R}^a\text{)C(=O)NR}^a\text{R}^a$, $-\text{N(R}^a\text{)C(=NR}^a\text{)NR}^a\text{R}^a$, $-\text{N(R}^a\text{)S(=O)}_2\text{R}^a$, $-\text{N(R}^a\text{)S(=O)}_2\text{NR}^a\text{R}^a$, $-\text{NR}^a\text{C}_{2-6}\text{alkylNR}^a\text{R}^a$ and $-\text{NR}^a\text{C}_{2-6}\text{alkylOR}^a$;
 R^{10} is H, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{haloalkyl}$, cyano, nitro, CO_2R^a , $\text{C(=O)NR}^a\text{R}^a$, $-\text{C(=NR}^a\text{)NR}^a\text{R}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)R}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)OR}^a$, $-\text{S(=O)}_2\text{N(R}^a\text{)C(=O)NR}^a\text{R}^a$, $-\text{S(=O)R}^b$, $-\text{S(=O)}_2\text{R}^b$ or $\text{S(=O)}_2\text{NR}^a\text{R}^a$;
 R^{11} is H or $\text{C}_{1-4}\text{alkyl}$;
 R^a is independently, at each instance, H or R^b ; and
 R^b is independently, at each instance, phenyl, benzyl or $\text{C}_{1-6}\text{alkyl}$, the phenyl, benzyl and $\text{C}_{1-6}\text{alkyl}$ being substituted by 0, 1, 2 or 3 substituents selected from halo, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-3}\text{haloalkyl}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{NH}_2$, $-\text{NHC}_{1-4}\text{alkyl}$, $-\text{N(C}_{1-4}\text{alkyl)C}_{1-4}\text{alkyl}$.

[00115] In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $\text{C(R}^9\text{)}$ and X^2 is N.

[00116] In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $\text{C(R}^9\text{)}$ and X^2 is $\text{C(R}^{10}\text{)}$.

[00117] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl substituted by 0 or 1 R^2 substituents, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, $\text{C}_{1-4}\text{alkyl}$, $\text{OC}_{1-4}\text{alkyl}$, $\text{OC}_{1-4}\text{haloalkyl}$, $\text{NHC}_{1-4}\text{alkyl}$, $\text{N(C}_{1-4}\text{alkyl)C}_{1-4}\text{alkyl}$ and $\text{C}_{1-4}\text{haloalkyl}$.

[00118] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is phenyl.

[00119] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is phenyl substituted by R², and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl.

[00120] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is selected from 2-methylphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-fluorophenyl and 2-methoxyphenyl.

[00121] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is phenoxy.

[00122] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl.

[00123] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 1 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl.

[00124] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or

1 R² substituents, and the ring is additionally substituted by 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl.

[00125] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S.

[00126] In another embodiment, in conjunction with any of the above or below embodiments, R¹ is selected from pyridyl and pyrimidinyl.

[00127] In another embodiment, in conjunction with any of the above or below embodiments, R³ is selected from halo, C₁₋₄haloalkyl, cyano, nitro, —C(O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)₂R^a, —OC₂₋₆alkylNR^aR^a, —OC₂₋₆alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)₂R^a, —S(=O)NR^aR^a, —S(=O)₂N(R^a)C(=O)R^a, —S(=O)₂N(R^a)C(O)OR^a, —S(=O)₂N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)₂R^a, —N(R^a)S(=O)₂NR^aR^a, —NR^aC₂₋₆alkylNR^aR^a, —NR^a, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl.

[00128] In another embodiment, in conjunction with any of the above or below embodiments, R³ is H.

[00129] In another embodiment, in conjunction with any of the above or below embodiments, R³ is selected from F, Cl, C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C₁₋₆alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C₁₋₆haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and C₁₋₆alkyl.

[00130] In another embodiment, in conjunction with any of the above or below embodiments, R⁵ is, independently, in each instance, H, halo, C₁₋₆alkyl, C₁₋₄haloalkyl, or C₁₋₆alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl; or both R⁵ groups together form a C₃₋

6spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl.

[00131] In another embodiment, in conjunction with any of the above or below embodiments, R⁵ is H.

[00132] In another embodiment, in conjunction with any of the above or below embodiments, one R⁵ is S-methyl, the other is H.

[00133] In another embodiment, in conjunction with any of the above or below embodiments, at least one R⁵ is halo, C₁₋₆alkyl, C₁₋₄haloalkyl, or C₁₋₆alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₋₄alkyl, C₁₋₄alkyl, C₁₋₃haloalkyl, OC₁₋₄alkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)C₁₋₄alkyl.

[00134] In another embodiment, in conjunction with any of the above or below embodiments, R⁶ is H.

[00135] In another embodiment, in conjunction with any of the above or below embodiments, R⁶ is F, Cl, cyano or nitro.

[00136] In another embodiment, in conjunction with any of the above or below embodiments, R⁷ is H.

[00137] In another embodiment, in conjunction with any of the above or below embodiments, R⁷ is F, Cl, cyano or nitro.

[00138] In another embodiment, in conjunction with any of the above or below embodiments, R⁸ is selected from H, CF₃, C₁₋₃alkyl, Br, Cl and F.

[00139] In another embodiment, in conjunction with any of the above or below embodiments, R⁸ is selected from H.

[00140] In another embodiment, in conjunction with any of the above or below embodiments, R⁸ is selected from CF₃, C₁₋₃alkyl, Br, Cl and F.

[00141] In another embodiment, in conjunction with any of the above or below embodiments, R⁹ is H.

[00142] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is selected from halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $C_{1-6}alkyl$, phenyl, benzyl, heteroaryl and heterocycle, wherein the $C_{1-6}alkyl$, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$.

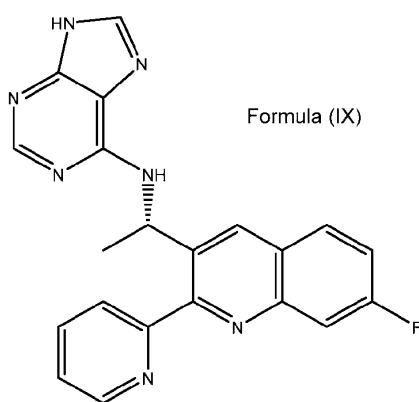
[00143] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$.

[00144] In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is H.

[00145] In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is cyano, nitro, CO_2R^a , $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$.

[00146] In another embodiment, in conjunction with any of the above or below embodiments, R^{11} is H.

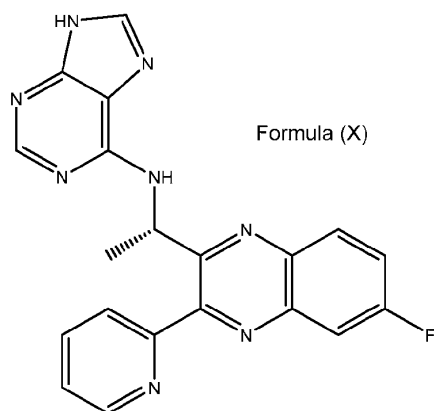
[00147] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (IX):



or a pharmaceutically-acceptable salt thereof

[00148] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is (*S*)-*N*-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

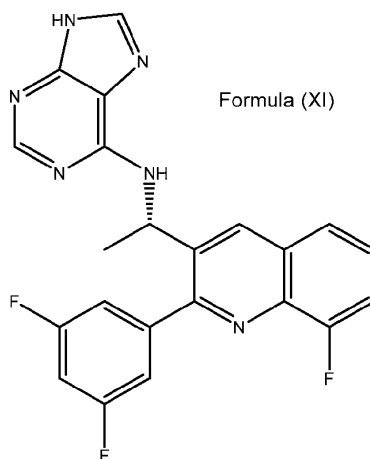
[00149] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (X):



or a pharmaceutically-acceptable salt thereof

[00150] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is (*S*)-*N*-(1-(6-fluoro-3-(pyridin-2-yl)quinoxalin-2-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

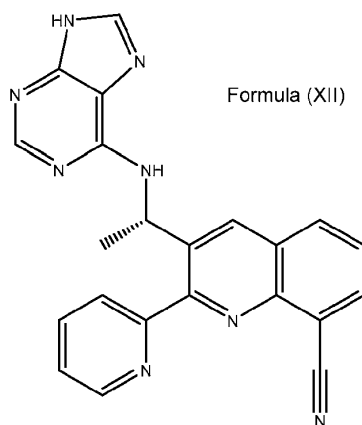
[00151] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (XI):



or a pharmaceutically-acceptable salt thereof.

[00152] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is (*S*)-*N*-(1-(2-(3,5-difluorophenyl)-8-fluoroquinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

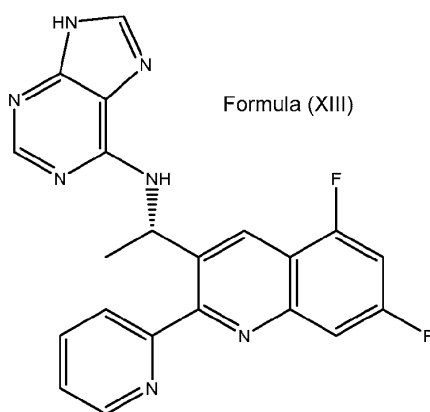
[00153] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (XII):



or a pharmaceutically-acceptable salt thereof

[00154] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is (*S*)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-2-(pyridin-2-yl)quinoline-8-carbonitrile or a pharmaceutically-acceptable salt thereof.

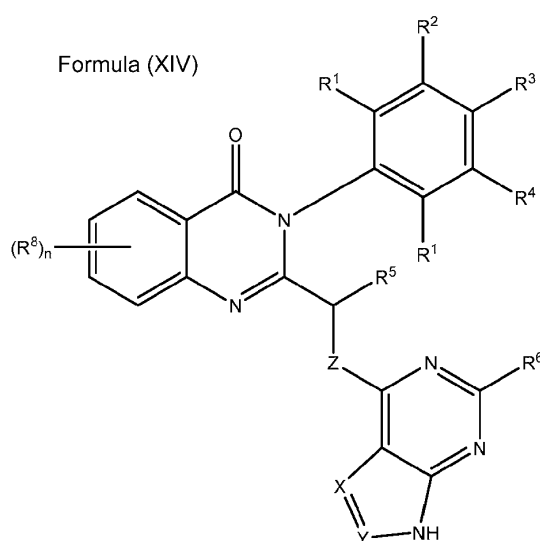
[00155] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (XIII):



or a pharmaceutically-acceptable salt thereof

[00156] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is (*S*)-*N*-(1-(5,7-difluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00157] In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 7,932,260 and 8,207,153, the disclosure of which is incorporated by reference herein. In an exemplary embodiment, the PI3K inhibitor or PI3K- δ inhibitor is a compound of Formula (XIV):



wherein

X and Y, independently, are N or CR^c;

Z is N—R⁷ or O;

R¹ are the same and are hydrogen, halo, or C₁₋₃alkyl;

R² and R³, independently, are hydrogen, halo, or C₁₋₃alkyl;

R⁴ is hydrogen, halo, OR^a, CN, C₂₋₆alkynyl, C(=O)R^a, C(=O)NR^aR^b, C₃₋₆heterocycloalkyl, C₁₋₃alkyleneC₃₋₆heterocycloalkyl, OC₁₋₃alkyleneOR^a, OC₁₋₃alkyleneNR^aR^b, OC₁₋₃alkyleneC₃₋₆cycloalkyl, OC₃₋₆heterocycloalkyl, OC₁₋₃alkyleneC≡CH, or OC₁₋₃alkyleneC(=O)NR^aR^b;

R⁵ is C₁₋₃alkyl, CH₂CF₃, phenyl, CH₂C≡CH, C₁₋₃alkyleneOR^c, C₁₋₄alkyleneNR^aR^b, or C₁₋₄alkyleneNHC(=O)OR^a;

R⁶ is hydrogen, halo, or NR^aR^b;

R^7 is hydrogen or R^5 and R^7 are taken together with the atoms to which they are attached to form a five- or six-membered saturated ring;

R^8 is C_{1-3} alkyl, halo, CF_3 , or CH_2C_{3-6} heterocycloalkyl;

n is 0, 1, or 2;

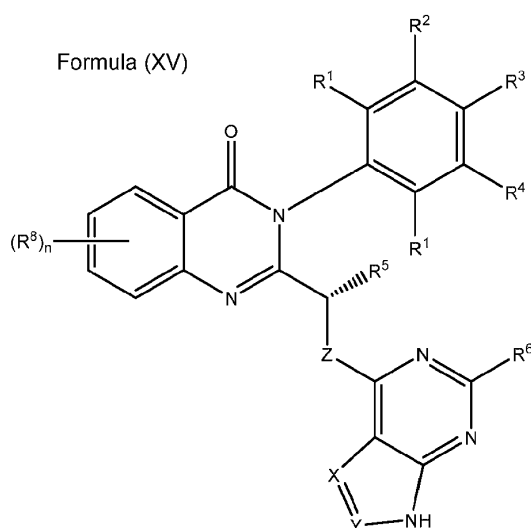
R^a is hydrogen, C_{1-4} alkyl, or $CH_2C_6H_5$;

R^b is hydrogen or C_{1-3} alkyl; and

R^c is hydrogen, C_{1-3} alkyl, or halo,

wherein when the R^1 groups are different from hydrogen, R^2 and R^4 are the same; or a pharmaceutically acceptable salt, or prodrug, or solvate (e.g., hydrate) thereof.

[00158] In a preferred embodiment, the PI3K inhibitor or PI3K- δ inhibitor is an enantiomer of Formula (XIV), as shown in Formula (XV):



wherein X , Y , Z , R^1 through R^8 , R^a , R^b , R^c , and n are as defined above for Formula (XIV).

[00159] In various embodiments exhibiting increased potency relative to other compounds, R^8 is C_{1-3} alkyl, F, Cl, or CF_3 . Alternatively, in such embodiments, n is 0 (such that there is no R^8 substituent).

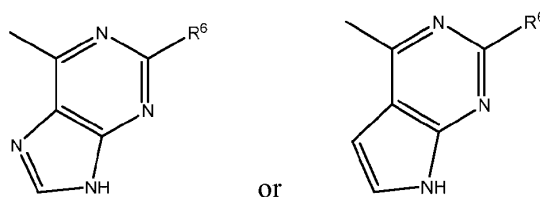
[00160] In other embodiments exhibiting such increased potency, X and Y , independently, are N or CH. In further embodiment exhibiting increased potency, X is N and Y is CH.

Alternatively, X and Y may also both be CH. In further embodiments exhibiting increased potency, R⁶ is hydrogen, halo, or NH₂.

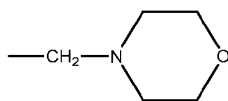
[00161] Unexpectedly, potency against PI3K-δ is conserved when R¹ is the same. In structural formulae (I) and (II), R² and R⁴ may differ provided that R¹ is H. When R¹ is H, free rotation is unexpectedly permitted about the bond connecting the phenyl ring substituent to the quinazoline ring, and the compounds advantageously do not exhibit atropisomerism (i.e., multiple diastereomer formation is avoided). Alternatively, R² and R⁴ can be the same such that the compounds advantageously do not exhibit atropisomerism.

[00162] As used with respect to Formula (XIV) and Formula (XV), the term “alkyl” is defined as straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms, e.g., methyl, ethyl, and straight chain and branched propyl and butyl groups. The terms “C₁₋₃alkylene” and “C₁₋₄alkylene” are defined as hydrocarbon groups containing the indicated number of carbon atoms and one less hydrogen than the corresponding alkyl group. The term “C₂₋₆alkynyl” is defined as a hydrocarbon group containing the indicated number of carbon atoms and a carbon-carbon triple bond. The term “C₃₋₆cycloalkyl” is defined as a cyclic hydrocarbon group containing the indicated number of carbon atoms. The term “C₂₋₆heterocycloalkyl” is defined similarly as cycloalkyl except the ring contains one or two heteroatoms selected from the group consisting of O, NR^a, and S. The term “halo” is defined as fluoro, bromo, chloro, and iodo.

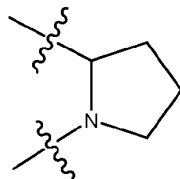
[00163] In preferred embodiments, Z is N—R⁷, and the bicyclic ring system containing X and Y is:



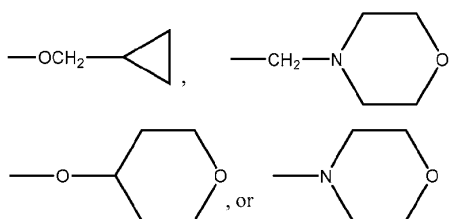
[00164] In other preferred embodiments, R¹ is hydrogen, fluoro, chloro, methyl, or



and R^2 is hydrogen, methyl, chloro, or fluoro; R^3 is hydrogen or fluoro; R^6 is NH_2 , hydrogen, or fluoro; R^7 is hydrogen or R^5 and R^7 are taken together to form

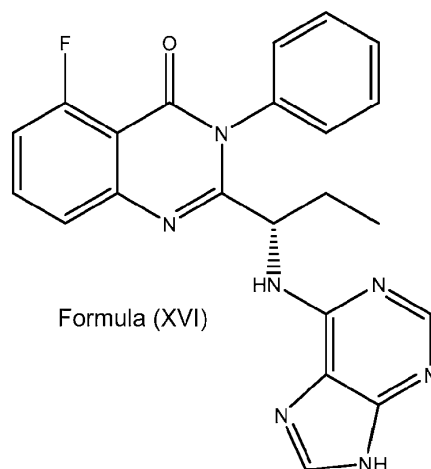


R^8 is methyl, trifluoromethyl, chloro, or fluoro; R^4 is hydrogen, fluoro, chloro, OH, OCH_3 , $OCH_2C\equiv CH$, $O(CH_2)_2N(CH_3)_2$, $C(=O)CH_3$, $C\equiv CH$, CN, $C(=O)NH_2$, $OCH_2C(=O)NH_2$, $O(CH_2)_2OCH_3$, $O(CH_2)_2N(CH_3)_2$,



and R^5 is methyl, ethyl, propyl, phenyl, CH_2OH , $CH_2OCH_2C_6H_5$, CH_2CF_3 , $CH_2OC(CH_3)_3$, $CH_2C\equiv CH$, $(CH_2)_3N(C_2H_5)_2$, $(CH_2)_3NH_2$, $(CH_2)_4NH_2$, $(CH_2)_3NHC(=O)OCH_2C_6H_5$, or $(CH_2)_4NHC(=O)OCH_2C_6H_5$; R^c is hydrogen, methyl, fluoro, or bromo; and n is 0 or 1.

[00165] In a preferred embodiment, the PI3K inhibitor or PI3K- δ inhibitor is the compound of Formula (XVI):



Formula (XVI)

or a pharmaceutically-acceptable salt thereof.

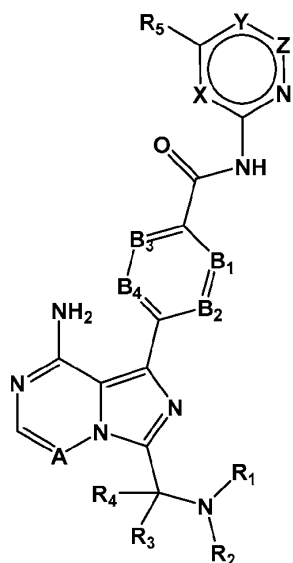
[00166] In a preferred embodiment, the PI3K inhibitor or PI3K- δ inhibitor is (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one or a pharmaceutically-acceptable salt thereof.

[00167] In an embodiment, the PI3K inhibitor or PI3K- δ inhibitor is 4(3H)-quinazolinone, 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]-5-fluoro-3-phenyl-2-[(1S)-1-[(7H-purin-6-yl)amino]propyl]quinazolin-4(3H)-one or a pharmaceutically-acceptable salt thereof.

[00168] Other PI3K inhibitors suitable for use in the described combination with a BTK inhibitor also include, but are not limited to, those described in, for example, U.S. Patent No. 8,193,182 and U.S. Published Application Nos. 2013/0267521; 2013/0053362; 2013/0029984; 2013/0029982; 2012/0184568; and 2012/0059000, the disclosures of each of which are incorporated by reference in their entireties.

BTK Inhibitors

[00169] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XVII):



Formula (XVII)

or a pharmaceutically acceptable salt thereof,

wherein:

X is CH, N, O or S;

Y is C(R₆), N, O or S;

Z is CH, N or bond;

A is CH or N;

B₁ is N or C(R₇);

B₂ is N or C(R₈);

B₃ is N or C(R₉);

B₄ is N or C(R₁₀);

R₁ is R₁₁C(=O), R₁₂S(=O), R₁₃S(=O)₂ or (1-6C)alkyl optionally substituted with R₁₄;

R₂ is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R₃ is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R₂ and R₃ form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R₄ is H or (1-3C)alkyl;

R₅ is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R₅ is (6-10C)aryl or (2-6C)heterocycloalkyl;

R₆ is H or (1-3C)alkyl; or

R₅ and R₆ together may form a (3-7C)cycloalkenyl or (2-6C)heterocycloalkenyl, each optionally substituted with (1-3C)alkyl or one or more halogens;

R₇ is H, halogen, CF₃, (1-3C)alkyl or (1-3C)alkoxy;

R₈ is H, halogen, CF₃, (1-3C)alkyl or (1-3C)alkoxy; or

R₇ and R₈ together with the carbon atoms they are attached to, form (6-10C)aryl or (1-9C)heteroaryl;

R₉ is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R₁₀ is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R₁₁ is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl, where each alkyl, alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl; or R₁₁ is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

R₁₁ is (1-5C)heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen or cyano;

R₁₂ and R₁₃ are independently selected from the group consisting of (2-6C)alkenyl or (2-6C)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl; or a (1-5C)heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen and cyano; and

R₁₄ is independently selected from the group consisting of halogen, cyano, (2-6C)alkenyl and (2-6C)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl and (3-7C)heterocycloalkyl;

with the proviso that:

0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;

when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from

X, Y can not be O or S;

when Z is C or N then Y is C(R6) or N and X is C or N;

0 to 2 atoms of B1, B2, B3 and B4 are N;

with the terms used having the following meanings:

(1-2C)alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl,

(1-3C)alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

(1-4C)alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (1-3C)alkyl groups being preferred;

(1-5C)alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and isopentyl, (1-4C)alkyl groups being preferred. (1-6C)Alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (1-5C)alkyl groups are preferred, (1-4C)alkyl being most preferred;

(1-2C)alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

(1-3C)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-2C)alkoxy groups are preferred;

(1-4C)alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-3C)alkoxy groups are preferred, (1-2C)alkoxy groups being most preferred;

(2-4C)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;

(2-6C)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, (2-4C)alkenyl groups being most preferred;

(2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butylnyl;

- (2-6C)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl. (2-4C)alkynyl groups are preferred; (3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
- (3-7C)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;
- (2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; also preferred are piperidine, morpholine, pyrrolidine and piperazine; with the most preferred (2-6C)heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;
- (3-7C)heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O; preferred (3-7C) heterocycloalkyl groups are azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (3-7C)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;
- (3-7C)cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;
- (6-10C)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred (6-10C)aryl group is phenyl;
- (1-5C)heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (1-5C)heteroaryl may optionally be substituted; preferred (1-5C)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, a more preferred (1-5C)heteroaryl is pyrimidyl;
- (1-9C)heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (1-9C)heteroaryl may optionally be substituted; preferred (1-9C)heteroaryl groups are quinoline, isoquinoline and indole;

[(1-4C)alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; preferred [(1-4C)alkyl]amino group is methylamino;

di[(1-4C)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; preferred di[(1-4C)alkyl]amino group is dimethylamino;

halogen means means fluorine, chlorine, bromine or iodine;

(1-3C)alkyl-C(0)-S-(1-3C)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

(3-7C)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred (3-7C)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; cyclohexenyl groups are most preferred;

(2-6C)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; preferred (2-6C)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl group.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula (XVII) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

The term "substituted" means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. "Stable compound" or "stable structure" is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

[00170] In an exemplary embodiment of Formula (XVII), B₁ is C(R₇); B₂ is C(R₈); B₃ is C(R₉); B₄ is C(R₁₀); R₇, R₉, and R₁₀ are each H; and R₈ is hydrogen or methyl.

[00171] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

[00172] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyridazyl.

[00173] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

[00174] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is pyridyl.

[00175] In an exemplary embodiment of Formula (XVII), R₅ is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

[00176] In an exemplary embodiment of Formula (XVII), R₅ is hydrogen.

[00177] In an exemplary embodiment of Formula (XVII), R₂ and R₃ together form a heterocycloalkyl ring selected from the group consisting of azetidiny, pyrrolidiny, piperidiny, homopiperidiny and morpholiny, optionally substituted with one or more of fluoro, hydroxyl, (1-3C)alkyl and (1-3C)alkoxy.

[00178] In an exemplary embodiment of Formula (XVII), R₂ and R₃ together form a heterocycloalkyl ring selected from the group consisting of azetidiny, pyrrolidiny and piperidiny.

[00179] In an exemplary embodiment of Formula (XVII), R₂ and R₃ together form a pyrrolidiny ring.

[00180] In an exemplary embodiment of Formula (XVII), R₁ is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-

7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl] amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl.

[00181] In an exemplary embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X is N; Y and Z are CH; R₅ is CH₃; A is N; R₂, R₃ and R₄ are H; and R₁ is CO-CH₃.

[00182] In an exemplary embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₅ is CH₃; A is N; R₂, R₃ and R₄ are H; and R₁ is CO-CH₃.

[00183] In an exemplary embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₅ is CH₃; A is CH; R₂ and R₃ together form a piperidinyl ring; R₄ is H; and R₁ is CO-ethenyl.

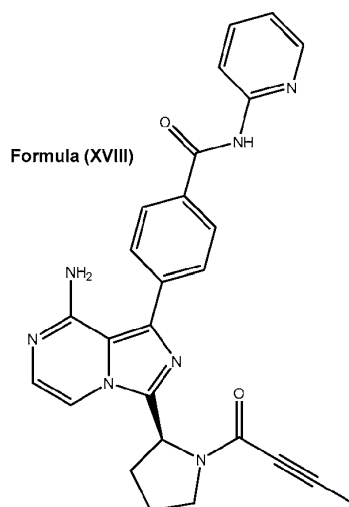
[00184] In an exemplary embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X, Y and Z are CH; R₅ is H; A is CH; R₂ and R₃ together form a pyrrolidinyl ring; R₄ is H; and R₁ is CO-propynyl.

[00185] In an exemplary embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X, Y and Z are CH; R₅ is CH₃; A is CH; R₂ and R₃ together form a piperidinyl ring; R₄ is H; and R₁ is CO-propynyl.

[00186] In an exemplary embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₅ is H; A is CH; R₂ and R₃ together form a morpholinyl ring; R₄ is H; and R₁ is CO-ethenyl.

[00187] In an exemplary embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₅ is CH₃; A is CH; R₂ and R₃ together form a morpholinyl ring; R₄ is H; and R₁ is CO-propynyl.

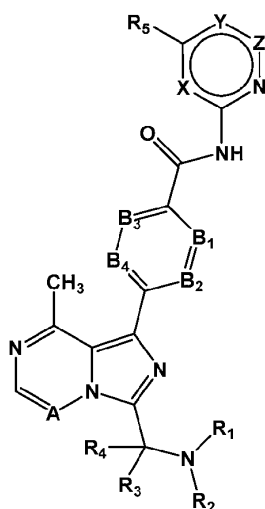
[00188] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XVIII):



or a pharmaceutically-acceptable salt thereof. The preparation of this compound is described at Example 6 of International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference. The preparation of this compound and related structures are described in the Examples of International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference.

[00189] In an exemplary embodiment, the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or pharmaceutically-acceptable salt thereof.

[00190] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XIX) or a pharmaceutically-acceptable salt of a compound of Formula (XIX):



Formula (XIX)

In Formula (XIX) the substituents are defined as

X is CH, N, O or S;

Y is C(R₆), N, O or S;

Z is CH, N or bond;

A is CH or N;

B₁ is N or C(R₇);

B₂ is N or C(R₈);

B₃ is N or C(R₉);

B₄ is N or C(R₁₀);

R₁ is R₁₁C(O), R₁₂S(O), R₁₃SO₂ or (1-6C)alkyl optionally substituted with R₁₄;

R₂ is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R₃ is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R₂ and R₃ form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R₄ is H or (1-3C)alkyl;

R₅ is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl; all alkyl groups of R₅ are optionally substituted with one or more halogen; or R₅ is (6-10C)aryl or (2-6C)heterocycloalkyl;

R₆ is H or (1-3C)alkyl; or R₅ and R₆ together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R₇ is H, halogen, CF₃, (1-3C)alkyl or (1-3C)alkoxy;

R₈ is H, halogen, CF₃, (1-3C)alkyl or (1-3C)alkoxy; or

R₇ and R₈ together with the carbon atoms they are attached to, form (6-10C)aryl or (1-5C)heteroaryl;

R₉ is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R₁₀ is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R₁₁ is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl, or

R₁₁ is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

R₁₁ is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

R₁₂ and R₁₃ are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R₁₄ is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
- when Z is C or N then Y is C(R₆) or N and X is C or N;
- 0 to 2 atoms of B₁, B₂, B₃ and B₄ are N;

with the terms used having the following meanings:

- (1-3C)alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;
- (1-4C)alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (1-3C)alkyl groups being preferred;
- (1-6C)alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (1-5C)alkyl groups are preferred, (1-4C)alkyl being most preferred;
- (1-2C)alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;
- (1-3C)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined, with (1-2C)alkoxy groups preferred;
- (2-3C)alkenyl means an alkenyl group having 2-3 carbon atoms, such as ethenyl or 2-propenyl;
- (2-4C)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;
- (2-6C)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, with (2-4C)alkenyl groups preferred, and (2-3C)alkenyl groups even more preferred;
- (2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;
- (2-3C)alkynyl means an alkynyl group having 2-3 carbon atoms, such as ethynyl or 2-propynyl;
- (2-6C)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butylnyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl, with (2-4C)alkynyl groups preferred, and (2-3C)alkynyl groups more preferred;
- (3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
- (3-7C)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;
- (2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O;

preferred groups are piperidine, morpholine, pyrrolidine and piperazine; a most preferred (2-6C)heterocycloalkyl is pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(3-7C)heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3- 5 carbon atoms, and one or two heteroatoms selected from N, O and/or S; preferred heteroatoms are N or O; preferred (3-7C) heterocycloalkyl groups are azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (3-7C)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; even more preferred are piperidine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(3-7C)cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

(6-10C)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred (6-10C)aryl group is phenyl;

(1-5C)heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S, wherein the (1-5C)heteroaryl may optionally be substituted.; preferred (1-5C)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, and the more preferred (1-5C)heteroaryl is pyrimidyl;

[(1-4C)alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; the preferred [(1-4C)alkyl]amino group is methylamino;

di[(1-4C)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; the preferred di[(1-4C)alkyl]amino group is dimethylamino;

halogen means means fluorine, chlorine, bromine or iodine;

(1-3C)alkyl-C(O)-S-(1-3C)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

(3-7C)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred (3-7C)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; and cyclohexenyl groups are most preferred;

(2-6C)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; the preferred (2-6C)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl groups.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

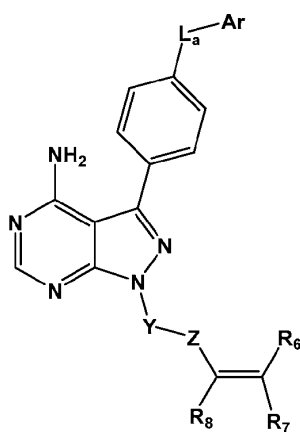
A circle in a ring of Formula (XIX) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

The term "substituted" means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. "Stable compound" or "stable structure" is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties. In one aspect the invention relates to a compound according to formula I wherein B₁ is C(R₇); B₂ is C(R₈); B₃ is C(R₉) and B₄ is C(R₁₀).

[00191] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XX):



Formula (XX)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Z is $C(=O)$, $OC(=O)$, $NRC(=O)$, $C(=S)$, $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

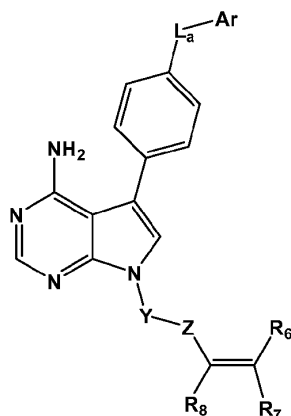
R^7 and R^8 are each independently H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

R is H or C_1 - C_6 alkyl.

[00192] In an exemplary embodiment, the BTK inhibitor is ibrutinib or a pharmaceutically-acceptable salt thereof.

[00193] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXI):



Formula (XXI)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

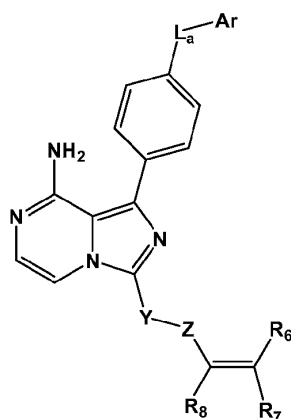
Z is C(=O), OC(=O), NRC(=O), C(=S), S(=O)_x, OS(=O)_x or NRS(=O)_x, where x is 1 or 2;

R⁷ and R⁸ are each H; or R⁷ and R⁸ taken together form a bond;

R⁶ is H; and

R is H or C₁-C₆alkyl.

[00194] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXII):



Formula (XXII)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH₂, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

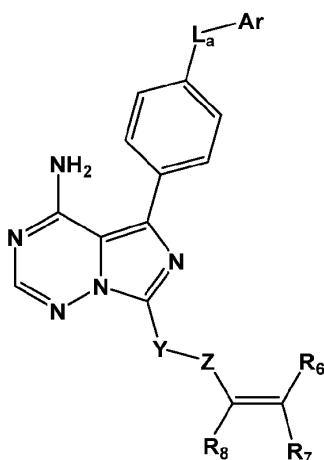
Z is C(=O), OC(=O), NRC(=O), C(=S), S(=O)_x, OS(=O)_x or NRS(=O)_x, where x is 1 or 2;

R⁷ and R⁸ are each H; or R⁷ and R⁸ taken together form a bond;

R⁶ is H; and

R is H or C₁-C₆alkyl.

[00195] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXIII):



Formula (XXIII)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Z is $C(=O)$, $OC(=O)$, $NRC(=O)$, $C(=S)$, $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

R is H or C_1 - C_6 alkyl.

[00196] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXIV):



Formula (XXIV)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is aryl¹, heteroaryl¹, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one to five independent G^1 substituents;

R^1 is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, or heterobicycloalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

G^1 and G^{41} are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, $-CN$, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C=O)R^3$, $NR^2(C=O)OR^3$, $NR^2(C=O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C=S)OR^2$, $-(C=O)SR^2$, $-NR^2(C=NR^3)NR^{2a}R^{3a}$, $-NR^2(C=NR^3)OR^{2a}$, $-NR^2(C=NR^3)SR^{3a}$, $-O(C=O)OR^2$, $-O(C=O)NR^2R^3$, $-O(C=O)SR^2$, $-S(C=O)OR^2$, $-S(C=O)NR^2R^3$, $C_{0-10}alkyl$, $C_{2-10}alkenyl$, $C_{2-10}alkynyl$, $C_{1-10}alkoxyC_{1-10}alkyl$, $C_{1-10}alkoxyC_{2-10}alkenyl$, $C_{1-10}alkoxyC_{2-10}alkynyl$, $C_{1-10}alkylthioC_{1-10}alkyl$, $C_{1-10}alkylthioC_{2-10}alkenyl$, $C_{1-10}alkylthioC_{2-10}alkynyl$, $cycloC_{3-8}alkyl$, $cycloC_{3-8}alkenyl$, $cycloC_{3-8}alkylC_{1-10}alkyl$, $cycloC_{3-8}alkenylC_{1-10}alkyl$, $cycloC_{3-8}alkylC_{2-10}alkenyl$, $cycloC_{3-8}alkenylC_{2-10}alkenyl$, $cycloC_{3-8}alkylC_{2-10}alkynyl$, $cycloC_{3-8}alkenylC_{2-10}alkynyl$, $cycloC_{3-8}alkenylC_{2-10}alkynyl$, $heterocyclyl-C_{0-10}alkyl$, $heterocyclyl-C_{2-10}alkenyl$, or $heterocyclyl-C_{2-10}alkynyl$, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or $-(X^1)_n-(Y^1)_m-R^4$; or aryl- $C_{0-10}alkyl$, aryl- $C_{2-10}alkenyl$, or aryl- $C_{2-10}alkynyl$, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or hetaryl- $C_{0-10}alkyl$, hetaryl- $C_{2-10}alkenyl$, or hetaryl- $C_{2-10}alkynyl$, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j3a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j3a}R^{222}$, $-SO_2NR^{222}R^{333}$,

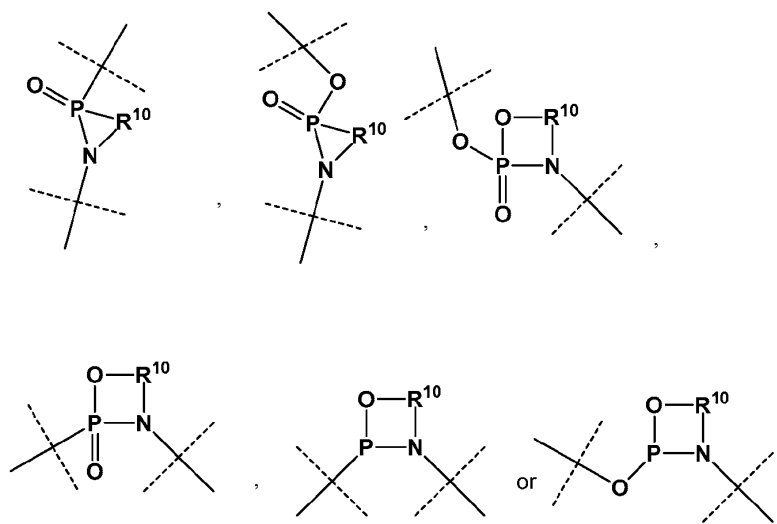
NR²²²(C=O)R³³³, NR²²²(C=O)OR³³³, NR²²²(C=O)NR²²²R³³³, NR²²²S(O)_{j3a}R³³³, -(C=S)OR²²², -(C=O)SR²²², -NR²²²(C=NR³³³)NR²²²aR³³³a, -NR²²²(C=NR³³³)OR^{222a}, -NR²²²(C=NR³³³)SR³³³a, -O(C=O)OR²²², -O(C=O)NR²²²R³³³, -O(C=O)SR²²², -S(C=O)OR²²², or -S(C=O)NR²²²R³³³ substituents;

G¹¹ is halo, oxo, -CF₃, -OCF₃, -OR²¹, -NR²¹R³¹(R^{3a1})_{j4}, -C(O)R²¹, -CO₂R²¹, -CONR²¹R³¹, -NO₂, -CN, -S(O)_{j4}R²¹, -SO₂NR²¹R³¹, NR²¹(C=O)R³¹, NR²¹(C=O)OR³¹, NR²¹(C=O)NR²¹R³¹, NR²¹S(O)_{j4}R³¹, -(C=S)OR²¹, -(C=O)SR²¹, -NR²¹(C=NR³¹)NR^{2a1}R^{3a1}, -NR²¹(C=NR³¹)OR^{2a1}, -NR²¹(C=NR³¹)SR^{3a1}, -O(C=O)OR²¹, -O(C=O)NR²¹R³¹, -O(C=O)SR²¹, -S(C=O)OR²¹, -S(C=O)NR²¹R³¹, -P(O)OR²¹OR³¹, C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋₁₀alkynyl, C₁₋₁₀alkylthioC₁₋₁₀alkyl, C₁₋₁₀alkylthioC₂₋₁₀alkenyl, C₁₋₁₀alkylthioC₂₋₁₀alkynyl, cycloC₃₋₈alkyl, cycloC₃₋₈alkenyl, cycloC₃₋₈alkylC₁₋₁₀alkyl, cycloC₃₋₈alkenylC₁₋₁₀alkyl, cycloC₃₋₈alkylC₂₋₁₀alkenyl, cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, or heterocyclyl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, oxo, -CF₃, -OCF₃, -OR²²²¹, -NR²²²¹R³³³¹(R^{333a1})_{j4a}, -C(O)R²²²¹, -CO₂R²²²¹, -CONR²²²¹R³³³¹, -NO₂, -CN, -S(O)_{j4a}R²²²¹, -SO₂NR²²²¹R³³³¹, NR²²²¹(C=O)R³³³¹, NR²²²¹(C=O)OR³³³¹, NR²²²¹(C=O)NR²²²¹R³³³¹, NR²²²¹S(O)_{j4a}R³³³¹, -(C=S)OR²²²¹, -(C=O)SR²²²¹, -NR²²²¹(C=NR³³³¹)NR^{222a1}R^{333a1}, -NR²²²¹(C=NR³³³¹)OR^{222a1}, -NR²²²¹(C=NR³³³¹)SR^{333a1}, -O(C=O)OR²²²¹, -O(C=O)NR²²²¹R³³³¹, -O(C=O)SR²²²¹, -S(C=O)OR²²²¹, -P(O)OR²²²¹OR³³³¹, or -S(C=O)NR²²²¹R³³³¹ substituents; or aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, or aryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR²²²¹, -NR²²²¹R³³³¹(R^{333a1})_{j5a}, -C(O)R²²²¹, -CO₂R²²²¹, -CONR²²²¹R³³³¹, -NO₂, -CN, -S(O)_{j5a}R²²²¹, -SO₂NR²²²¹R³³³¹, NR²²²¹(C=O)R³³³¹, NR²²²¹(C=O)OR³³³¹, NR²²²¹(C=O)NR²²²¹R³³³¹, NR²²²¹S(O)_{j5a}R³³³¹, -(C=S)OR²²²¹, -(C=O)SR²²²¹, -NR²²²¹(C=NR³³³¹)NR^{222a1}R^{333a1}, -NR²²²¹(C=NR³³³¹)OR^{222a1}, -NR²²²¹(C=NR³³³¹)SR^{333a1}, -O(C=O)OR²²²¹, -O(C=O)NR²²²¹R³³³¹, -O(C=O)SR²²²¹, -S(C=O)OR²²²¹, -P(O)OR²²²¹R³³³¹, or -S(C=O)NR²²²¹R³³³¹ substituents; or hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR²²²¹, -NR²²²¹R³³³¹(R^{333a1})_{j6a}, -C(O)R²²²¹, -CO₂R²²²¹, -CONR²²²¹R³³³¹, -NO₂, -CN, -S(O)_{j6a}R²²²¹, -SO₂NR²²²¹R³³³¹, NR²²²¹(C=O)R³³³¹, NR²²²¹(C=O)OR³³³¹,

$\text{NR}^{2221}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$, $\text{NR}^{2221}\text{S}(\text{O})_{j6a}\text{R}^{3331}$, $-(\text{C}=\text{S})\text{OR}^{2221}$, $-(\text{C}=\text{O})\text{SR}^{2221}$, -
 $\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{NR}^{222a1}\text{R}^{333a1}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{OR}^{222a1}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{SR}^{333a1}$, -
 $\text{O}(\text{C}=\text{O})\text{OR}^{2221}$, $-\text{O}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$, $-\text{O}(\text{C}=\text{O})\text{SR}^{2221}$, $-\text{S}(\text{C}=\text{O})\text{OR}^{2221}$, $-\text{P}(\text{O})\text{OR}^{2221}\text{OR}^{3331}$,
 or $-\text{S}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$ substituents; or G^{11} is taken together with the carbon to which it is
 attached to form a double bond which is substituted with R^5 and G^{111} ;
 R^2 , R^{2a} , R^3 , R^{3a} , R^{222} , R^{222a} , R^{333} , R^{333a} , R^{21} , R^{2a1} , R^{31} , R^{3a1} , R^{2221} , R^{222a1} , R^{3331} , and R^{333a1} are
 each independently equal to $\text{C}_{0-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{C}_{1-10}\text{alkoxyC}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkoxyC}_{2-10}\text{alkenyl}$, $\text{C}_{1-10}\text{alkoxyC}_{2-10}\text{alkynyl}$, $\text{C}_{1-10}\text{alkylthioC}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkylthioC}_{2-10}\text{alkenyl}$, $\text{C}_{1-10}\text{alkylthioC}_{2-10}\text{alkynyl}$, $\text{cycloC}_{3-8}\text{alkyl}$, $\text{cycloC}_{3-8}\text{alkenyl}$, $\text{cycloC}_{3-8}\text{alkylC}_{1-10}\text{alkyl}$, $\text{cycloC}_{3-8}\text{alkenylC}_{1-10}\text{alkyl}$, $\text{cycloC}_{3-8}\text{alkenylC}_{2-10}\text{alkenyl}$, $\text{cycloC}_{3-8}\text{alkenylC}_{2-10}\text{alkynyl}$, $\text{cycloC}_{3-8}\text{alkenylC}_{2-10}\text{alkynyl}$, $\text{heterocyclyl-C}_{0-10}\text{alkyl}$, $\text{heterocyclyl-C}_{2-10}\text{alkenyl}$, or $\text{heterocyclyl-C}_{2-10}\text{alkynyl}$, any of which is optionally
 substituted by one or more G^{111} substituents; or $\text{aryl-C}_{0-10}\text{alkyl}$, $\text{aryl-C}_{2-10}\text{alkenyl}$, or $\text{aryl-C}_{2-10}\text{alkynyl}$, $\text{hetaryl-C}_{0-10}\text{alkyl}$, $\text{hetaryl-C}_{2-10}\text{alkenyl}$, or $\text{hetaryl-C}_{2-10}\text{alkynyl}$, any of which is
 optionally substituted by one or more G^{111} substituents; or in the case of $-\text{NR}^2\text{R}^3(\text{R}^{3a})_{j1}$ or -
 $\text{NR}^{222}\text{R}^{333}(\text{R}^{333a})_{j1a}$ or $-\text{NR}^{222}\text{R}^{333}(\text{R}^{333a})_{j2a}$ or $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{333a1})_{j3a}$ or $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{333a1})_{j4a}$
 or $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{333a1})_{j5a}$ or $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{333a1})_{j6a}$, R^2 and R^3 or R^{222} and R^{333} or R^{2221} and
 R^{3331} taken together with the nitrogen atom to which they are attached form a 3-10 membered
 saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring,
 wherein said ring is optionally substituted by one or more G^{111} substituents;
 X^1 and Y^1 are each independently $-\text{O}-$, $-\text{NR}^7-$, $-\text{S}(\text{O})_{j7}-$, $-\text{CR}^5\text{R}^6-$, $-\text{N}(\text{C}(\text{O})\text{OR}^7)-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)-$,
 $-\text{N}(\text{SO}_2\text{R}^7)-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{N}(\text{R}^7)-$, $-\text{CH}(\text{NR}^7)-$, $-\text{CH}_2\text{N}(\text{C}(\text{O})\text{R}^7)-$, $-\text{CH}_2\text{N}(\text{C}(\text{O})\text{OR}^7)-$,
 $-\text{CH}_2\text{N}(\text{SO}_2\text{R}^7)-$, $-\text{CH}(\text{NHR}^7)-$, $-\text{CH}(\text{NHC}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{NHSO}_2\text{R}^7)-$, $-\text{CH}(\text{NHC}(\text{O})\text{OR}^7)-$,
 $-\text{CH}(\text{OC}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{OC}(\text{O})\text{NHR}^7)-$, $-\text{CH}=\text{CH}-$, $-\text{C.ident.C}-$, $-\text{C}(=\text{NOR}^7)-$, $-\text{C}(\text{O})-$, -
 $\text{CH}(\text{OR}^7)-$, $-\text{C}(\text{O})\text{N}(\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})\text{N}(\text{R}^7)-$, -
 $\text{N}(\text{R}^7)\text{C}(\text{O})\text{N}(\text{R}^7)-$, $-\text{NR}^7\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})\text{N}(\text{R}^7)-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^7)-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{S}(\text{O})-$, -
 $\text{N}(\text{C}(\text{O})\text{R}^7)\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})\text{N}(\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{N}(\text{R}^7)-$, $-\text{C}(\text{O})\text{N}(\text{R}^7)\text{C}(\text{O})-$, -
 $\text{S}(\text{O})\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{OS}(\text{O})\text{N}(\text{R}^7)-$, $-\text{OS}(\text{O})_2\text{N}(\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})\text{O}-$, -
 $\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})\text{C}(\text{O})-$, $-\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{C}(\text{O})-$, $-\text{SON}(\text{C}(\text{O})\text{R}^7)-$, $-\text{SO}_2\text{N}(\text{C}(\text{O})\text{R}^7)-$, -
 $\text{N}(\text{R}^7)\text{SON}(\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{SO}_2\text{N}(\text{R}^7)-$, $-\text{C}(\text{O})\text{O}-$, $-\text{N}(\text{R}^7)\text{P}(\text{OR}^8)\text{O}-$, $-\text{N}(\text{R}^7)\text{P}(\text{OR}^8)-$, -
 $\text{N}(\text{R}^7)\text{P}(\text{O})(\text{OR}^8)\text{O}-$, $-\text{N}(\text{R}^7)\text{P}(\text{O})(\text{OR}^8)-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)\text{O}-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)-$, -

$\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{O})(\text{OR}^8)\text{O}-$, $-\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})_2-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{OR}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{SO}_2\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{O}-$, $-\text{CH}(\text{R}^7)\text{S}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{OR}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{SO}_2\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{C}(=\text{NOR}^7)-$, $-\text{CH}(\text{R}^7)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{CH}(\text{OR}^7)-$, $-\text{CH}(\text{R}^7)\text{C}(\text{O})\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})_2-$, $-\text{CH}(\text{R}^7)\text{OC}(\text{O})\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{C}(\text{O})\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{NR}^7\text{C}(\text{O})\text{O}-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})_2\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)\text{S}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)\text{S}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{C}(\text{O})\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{S}(\text{O})_2\text{N}(\text{R}^7)\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{OS}(\text{O})\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{OS}(\text{O})_2\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{S}(\text{O})_2\text{C}(\text{O})-$, $-\text{CH}(\text{R}^7)\text{SON}(\text{C}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{SO}_2\text{N}(\text{C}(\text{O})\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{SON}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{SO}_2\text{N}(\text{R}^7)-$, $-\text{CH}(\text{R}^7)\text{C}(\text{O})\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{P}(\text{OR}^8)\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{P}(\text{OR}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{P}(\text{O})(\text{OR}^8)\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{R}^7)\text{P}(\text{O})(\text{OR}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)\text{O}-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)-$, $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{O})(\text{OR}^8)\text{O}-$, or $-\text{CH}(\text{R}^7)\text{N}(\text{C}(\text{O})\text{R}^7)\text{P}(\text{OR}^8)-$;

or X^1 and Y^1 are each independently represented by one of the following structural formulas:



R^{10} , taken together with the phosphinamide or phosphonamide, is a 5-, 6-, or 7-membered aryl, heteroaryl or heterocyclyl ring system;

R⁵, R⁶, and G¹¹¹ are each independently a C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋₁₀alkynyl, C₁₋₁₀alkylthioC₁₋₁₀alkyl, C₁₋₁₀alkylthioC₂₋₁₀alkenyl, C₁₋₁₀alkylthioC₂₋₁₀alkynyl, cycloC₃₋₈alkyl, cycloC₃₋₈alkenyl, cycloC₃₋₈alkylC₁₋₁₀alkyl, cycloC₃₋₈alkenylC₁₋₁₀alkyl, cycloC₃₋₈alkylC₂₋₁₀alkenyl, cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, or heterocyclyl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR⁷⁷, -NR⁷⁷R⁸⁷, -C(O)R⁷⁷, -CO₂R⁷⁷, -CONR⁷⁷R⁸⁷, -NO₂, -CN, -S(O)_{j5a}R⁷⁷, -SO₂NR⁷⁷R⁸⁷, -NR⁷⁷(C=O)R⁸⁷, -NR⁷⁷(C=O)OR⁸⁷, -NR⁷⁷(C=O)NR⁷⁸R⁸⁷, -NR⁷⁷S(O)_{j5a}R⁸⁷, -(C=S)OR⁷⁷, -(C=O)SR⁷⁷, -NR⁷⁷(C=NR⁸⁷)NR⁷⁸R⁸⁸, -NR⁷⁷(C=NR⁸⁷)OR⁷⁸, -NR⁷⁷(C=NR⁸⁷)SR⁷⁸, -O(C=O)OR⁷⁷, -O(C=O)NR⁷⁷R⁸⁷, -O(C=O)SR⁷⁷, -S(C=O)OR⁷⁷, -P(O)OR⁷⁷OR⁸⁷, or -S(C=O)NR⁷⁷R⁸⁷ substituents; or aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, or aryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR⁷⁷, -NR⁷⁷R⁸⁷, -C(O)R⁷⁷, -CO₂R⁷⁷, -CONR⁷⁷R⁸⁷, -NO₂, -CN, -S(O)_{j5a}R⁷⁷, -SO₂NR⁷⁷R⁸⁷, -NR⁷⁷(C=O)R⁸⁷, -NR⁷⁷(C=O)OR⁸⁷, -NR⁷⁷(C=O)NR⁷⁸R⁸⁷, -NR⁷⁷S(O)_{j5a}R⁸⁷, -(C=S)OR⁷⁷, -(C=O)SR⁷⁷, -NR⁷⁷(C=NR⁸⁷)NR⁷⁸R⁸⁸, -NR⁷⁷(C=NR⁸⁷)OR⁷⁸, -NR⁷⁷(C=NR⁸⁷)SR⁷⁸, -O(C=O)OR⁷⁷, -O(C=O)NR⁷⁷R⁸⁷, -O(C=O)SR⁷⁷, -S(C=O)OR⁷⁷, -P(O)OR⁷⁷OR⁸⁷, or -S(C=O)NR⁷⁷R⁸⁷ substituents; or hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR⁷⁷, -NR⁷⁷R⁸⁷, -C(O)R⁷⁷, -CO₂R⁷⁷, -CONR⁷⁷R⁸⁷, -NO₂, -CN, -S(O)_{j5a}R⁷⁷, -SO₂NR⁷⁷R⁸⁷, -NR⁷⁷(C=O)R⁸⁷, -NR⁷⁷(C=O)OR⁸⁷, -NR⁷⁷(C=O)NR⁷⁸R⁸⁷, -NR⁷⁷S(O)_{j5a}R⁸⁷, -(C=S)OR⁷⁷, -(C=O)SR⁷⁷, -NR⁷⁷(C=NR⁸⁷)NR⁷⁸R⁸⁸, -NR⁷⁷(C=NR⁸⁷)OR⁷⁸, -NR⁷⁷(C=NR⁸⁷)SR⁷⁸, -O(C=O)OR⁷⁷, -O(C=O)NR⁷⁷R⁸⁷, -O(C=O)SR⁷⁷, -S(C=O)OR⁷⁷, -P(O)OR⁷⁷OR⁸⁷, or -S(C=O)NR⁷⁷R⁸⁷ substituents; or R⁵ with R⁶ taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R⁶⁹; or R⁵ with R⁶ taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R⁶⁹;

R⁷ and R⁸ are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G¹¹¹ substituents;

R^4 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G^{41} substituents;

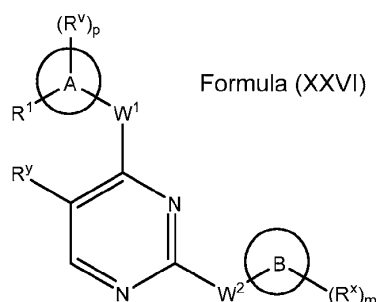
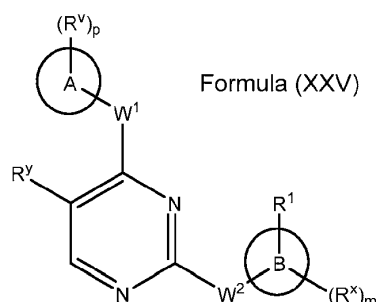
R^{69} is equal to halo, $-OR^{78}$, $-SH$, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-CONR^{78}R^{88}$, $-NO_2$, $-CN$, $-S(O)_2R^{78}$, $-SO_2NR^{78}R^{88}$, C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, or heterocyclyl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, or aryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-COOH$, C_{1-4} alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-COOH$, C_{1-4} alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or mono(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, mono(aryl)amino C_{1-6} alkyl, di(aryl)amino C_{1-6} alkyl, or $-N(C_{1-6}$ alkyl)- C_{1-6} alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-COOH$, C_{1-4} alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10} alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

R^{77} , R^{78} , R^{87} , R^{88} , R^{778} , and R^{888} are each independently C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl,

cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, heterocyclyl-C₂₋₁₀alkynyl, C₁₋₁₀alkylcarbonyl, C₂₋₁₀alkenylcarbonyl, C₂₋₁₀alkynylcarbonyl, C₁₋₁₀alkoxycarbonyl, C₁₋₁₀alkoxycarbonylC₁₋₁₀alkyl, monoC₁₋₆alkylaminocarbonyl, diC₁₋₆alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C₁₋₁₀alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C₁₋₁₀alkoxy, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl) substituents; or aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, or aryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(C₀₋₄alkyl), C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, haloC₁₋₁₀alkyl, haloC₂₋₁₀alkenyl, haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CON(C₀₋₄alkyl)(C₀₋₁₀alkyl), -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl) substituents; or hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(C₀₋₄alkyl), C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, haloC₁₋₁₀alkyl, haloC₂₋₁₀alkenyl, haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CON(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl) substituents; or mono(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, mono(aryl)aminoC₁₋₆alkyl, di(aryl)aminoC₁₋₆alkyl, or -N(C₁₋₆alkyl)-C₁₋₆alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(C₀₋₄alkyl), C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, haloC₁₋₁₀alkyl, haloC₂₋₁₀alkenyl, haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CON(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl) substituents; and

n, m, j1, j1a, j2a, j3a, j4, j4a, j5a, j6a, j7, and j8 are each independently equal to 0, 1, or 2.

[00197] In an exemplary embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 8,450,335 and 8,609,679, and U.S. Patent Application Publication Nos. 2010/0029610 A1, 2012/0077832 A1, 2013/0065879 A1, 2013/0072469 A1, and 2013/0165462 A1, the disclosures of which are incorporated by reference herein. In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI):



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated

heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is a warhead group;

R^y is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, C_{1-4} aliphatic, C_{1-4} haloaliphatic, $-\text{OR}$, $-\text{C}(\text{O})\text{R}$, or $-\text{C}(\text{O})\text{N}(\text{R})_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by $-\text{NR}^2-$, $-\text{N}(\text{R}^2)\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^2)-$, $-\text{N}(\text{R}^2)\text{SO}_2-$, $-\text{SO}_2\text{N}(\text{R}^2)-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}-$, $-\text{SO}-$ or $-\text{SO}_2-$;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or $-\text{C}(\text{O})\text{R}$, or:

R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring, or:

R^2 and R^y are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^v are independently selected from $-\text{R}$, halogen, $-\text{OR}$, $-\text{O}(\text{CH}_2)_q\text{OR}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{N}(\text{R})_2$, $-\text{SOR}$, $-\text{C}(\text{O})\text{R}$, $-\text{CO}_2\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{R}$, $-\text{NRC}(\text{O})\text{NR}_2$, $-\text{NRSO}_2\text{R}$, or $-\text{N}(\text{R})_2$, wherein q is 1-4; or:

R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, $-\text{CN}$, or C_{1-6} aliphatic; or

R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with

a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C₁₋₆ aliphatic.

[00198] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI), wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R¹ is -L-Y, wherein:

L is a covalent bond or a bivalent C₁₋₈ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO₂—, —SO₂N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO₂—, —C(=S)—, —C(=NR)—, —N=N—, or —C(=N₂)—;

Y is hydrogen, C₁₋₆ aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -Q-Z, oxo, NO₂, halogen, CN, or C₁₋₆ aliphatic, wherein:

Q is a covalent bond or a bivalent C₁₋₆ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —S—, —O—, —C(O)—, —SO—, or —SO₂—; and

Z is hydrogen or C₁₋₆ aliphatic optionally substituted with oxo, halogen, or CN;

R^y is hydrogen, halogen, —CN, —CF₃, C₁₋₄ aliphatic, C₁₋₄ haloaliphatic, —OR, —C(O)R, or —C(O)N(R)₂;

each R group is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

W¹ and W² are each independently a covalent bond or a bivalent C₁₋₃ alkylene chain wherein one methylene unit of W¹ or W² is optionally replaced by —NR²—, —N(R²)C(O)—, —C(O)N(R²)—, —N(R²)SO₂—, —SO₂N(R²)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO₂—;

R² is hydrogen, optionally substituted C₁₋₆ aliphatic, or —C(O)R, or:

R² and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or

R² and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^y are independently selected from $-R$, halogen, $-OR$, $-O(CH_2)_qOR$, $-CN$, $-NO_2$, $-SO_2R$, $-SO_2N(R)_2$, $-SOR$, $-C(O)R$, $-CO_2R$, $-C(O)N(R)_2$, $-NRC(O)R$, $-NRC(O)NR_2$, $-NRSO_2R$, or $-N(R)_2$, or:

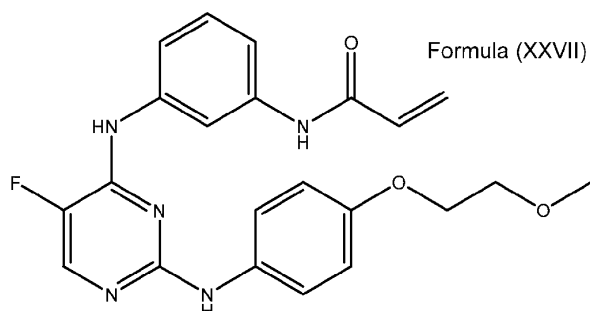
R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, $-CN$, or C_{1-6} aliphatic; or

R^y and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, $-CN$, or C_{1-6} aliphatic.

As defined generally above, Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is an optionally substituted phenyl group. In some embodiments, Ring A is an optionally substituted naphthyl ring or a bicyclic 8-10 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain other embodiments, Ring A is an optionally substituted 3-7 membered carbocyclic ring. In yet other embodiments, Ring A is an optionally substituted 4-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

In certain embodiments, Ring A is substituted as defined herein. In some embodiments, Ring A is substituted with one, two, or three groups independently selected from halogen, R^o , or $-(CH_2)_{0-4}OR^o$, or $-O(CH_2)_{0-4}R^o$, wherein each R^o is as defined herein. Exemplary substituents on Ring A include Br, I, Cl, methyl, $-CF_3$, $-C\equiv CH$, $-OCH_2phenyl$, $-OCH_2(fluorophenyl)$, or $-OCH_2pyridyl$.

[00199] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVII):



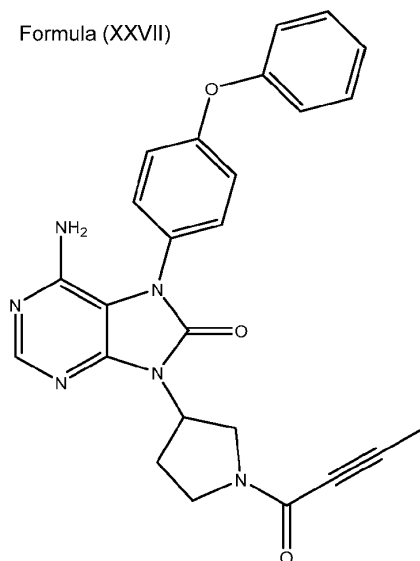
or a pharmaceutically acceptable salt thereof, or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of the besylate salt of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00200] In an exemplary embodiment, the BTK inhibitor is *N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00201] In an exemplary embodiment, the BTK inhibitor is (N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide), or a pharmaceutically acceptable salt thereof, or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of its besylate salt is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00202] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVIII):

Formula (XXVII)



6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one

or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00203] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00204] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00205] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-[(3S)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00206] BTK inhibitors suitable for use in the described combination with a PI3K inhibitor, a PI3K- γ inhibitor, and/or a PI3K- δ inhibitor also include, but are not limited to, those described in, for example, International Patent Application Publication Nos. WO 2013/010868; WO 2012/158843; WO 2012/135944; WO 2012/135937; U.S. Patent Application Publication No. 2011/0177011; and U.S. Patent Nos. 8,501,751; 8,476,284; 8,008,309; 7,960,396; 7,825,118; 7,732,454; 7,514,444; 7,459,554; 7,405,295; and 7,393,848, the disclosures of each of which are incorporated herein by reference.

Pharmaceutical Compositions

[00207] In selected embodiments, the invention provides pharmaceutical compositions for treating solid tumor cancers, lymphomas and leukemia.

[00208] In selected embodiments, the invention provides pharmaceutical compositions of a combination of a PI3K inhibitor, including a PI3K- γ or PI3K- δ inhibitor, and a BTK inhibitor for the treatment of disorders such as hyperproliferative disorder including but not limited to cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (*e.g.*, lymphoma and Kaposi's sarcoma) or viral-induced cancer. In some embodiments, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate (*e.g.*, benign prostatic hypertrophy (BPH)).

[00209] The invention further provides a composition for the prevention of blastocyte implantation in a mammal.

[00210] The invention also relates to a composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which can manifest as tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy,

retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00211] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a combination of a PI3K inhibitor, including a PI3K- γ or PI3K- δ inhibitor, and BTK inhibitor as the active ingredients, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[00212] The pharmaceutical compositions are administered as a combination of a PI3K inhibitor, including a PI3K- γ or PI3K- δ inhibitor, and a BTK inhibitor. Where desired, other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations for use in combination separately or at the same time.

[00213] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v.

[00214] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%,

2.25%, 2%, 1.75%, 1.50%, 1.25%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v.

[00215] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors of the invention is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v. v/v.

[00216] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors of the invention is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[00217] In selected embodiments, the amount of each of the PI3K and BTK inhibitors of the invention is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g,

0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g.

[00218] In selected embodiments, the amount of each of the PI3K and BTK inhibitors of the invention is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5 g, 3 g, 3.5 g, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g or 10 g.

[00219] Each of the PI3K and BTK inhibitors according to the invention is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently range from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[00220] Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing the indicated diseases or disorders can be tested using various animal models known in the art. Efficacy in treating, preventing and/or managing asthma can be assessed using the ova induced asthma model described, for example, in Lee *et al.*, J. Allergy Clin. Immunol. 118(2):403-9 (2006). Efficacy in treating, preventing and/or managing arthritis (*e.g.*, rheumatoid or psoriatic arthritis) can be assessed using the autoimmune animal models described in, for example, Williams *et al.*, Chem Biol, 17(2):123-34 (2010), WO 2009/088986, WO 2009/088880, and WO 2011/008302. Efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immuno-deficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke *et al.*, Clinics in Dermatology, 25: 596-605 (2007). Efficacy in treating, preventing and/or managing fibrosis or

fibrotic conditions can be assessed using the unilateral ureteral obstruction model of renal fibrosis, which is described, for example, in Chevalier *et al.*, *Kidney International* 75:1145-1152 (2009); the bleomycin induced model of pulmonary fibrosis described in, for example, Moore *et al.*, *Am. J. Physiol. Lung. Cell. Mol. Physiol.* 294:L152-L160 (2008); a variety of liver/biliary fibrosis models described in, for example, Chuang *et al.*, *Clin. Liver Dis.* 12:333-347 (2008) and Omenetti *et al.*, *Laboratory Investigation* 87:499-514 (2007) (biliary duct-ligated model); or any of a number of myelofibrosis mouse models such as described in Varicchio *et al.*, *Expert Rev. Hematol.* 2(3):315-334 (2009). Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto *et al.*, *J. Invest. Dermatol.* 112: 456-462 (1999). Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi *et al.*, *Arthritis & Rheumatism*, 60(10): 3118-3127 (2009). Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi *et al.*, *Lupus*, 19: 1029-1035 (2009); Ohl *et al.*, *Journal of Biomedicine and Biotechnology*, Article ID 432595 (2011); Xia *et al.*, *Rheumatology*, 50:2187-2196 (2011); Pau *et al.*, *PLoS ONE*, 7(5):e36761 (2012); Mustafa *et al.*, *Toxicology*, 290:156-168 (2011); Ichikawa *et al.*, *Arthritis and Rheumatism*, 62(2): 493-503 (2012); Ouyang *et al.*, *J. Mol. Med.* (2012); Rankin *et al.*, *Journal of Immunology*, 188:1656-1667 (2012). Efficacy in treating, preventing and/or managing Sjogren's syndrome can be assessed using various mouse models described, for example, in Chiorini *et al.*, *J. Autoimmunity*, 33: 190-196 (2009).

[00221] To explore the role of PI3K signaling in diffuse large B-cell lymphoma (“DLBCL”), several DLBCL cell lines of varying molecular profiles may be utilized. In an exemplary embodiment, a cellular growth inhibition assay used five cell lines, including four GCB (SU-DHL-4, SU-DHL-6, OCI-LY-8 and WSU-DLCL-2) and one ABC (Ri-1) subtype. In an exemplary embodiment, a cellular growth inhibition assay used five cell lines that were OCI-LY-3, OCI-LY-7, Pfeiffer, Toledo and U2932. In an exemplary embodiment, evidence of PI3K pathway inhibition is measured by reduction in phospho (p)-AKT. In an exemplary embodiment, the kinetics of pathway modulation was characterized by examination of phosphorylation of AKT, PRAS40 and S6 following a time-course of treatment by a PI3K-

inhibitor in selected cell lines. In one embodiment, upon B-cell receptor stimulation via antibody-induced crosslinking, some cell lines exhibited enhanced AKT phosphorylation.

[00222] In an exemplary embodiment, the combination effect of a PI3K inhibitor with a BTK inhibitor was observed in a cellular growth inhibition assay in the SU-DHL-4 cell line and in the OCI-LY-8 cell line with BCR crosslinking.

[00223] In one embodiment, provided herein is a method of treating, preventing and/or managing asthma. As used herein, "asthma" encompasses airway constriction regardless of the cause. Common triggers of asthma include, but are not limited to, exposure to an environmental stimulants (e.g., allergens), cold air, warm air, perfume, moist air, exercise or exertion, and emotional stress. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with asthma. Examples of the symptoms include, but are not limited to, severe coughing, airway constriction and mucus production.

[00224] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Oral Administration

[00225] In selected embodiments, the invention provides a pharmaceutical composition for oral administration containing the combination of a PI3K and BTK inhibitor, and a pharmaceutical excipient suitable for oral administration.

[00226] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of each of a PI3K and BTK inhibitor in combination and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of a fourth compound.

[00227] In selected embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount

of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00228] The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (*e.g.*, 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00229] Each of the PI3K and BTK inhibitors active ingredients can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation

desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00230] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00231] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00232] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to

form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algin, other celluloses, gums or mixtures thereof.

[00233] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00234] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00235] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00236] Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00237] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00238] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00239] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00240] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-

phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, chollysarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00241] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macroglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00242] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8

caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00243] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00244] In an exemplary embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use - *e.g.*, compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00245] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to

about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ϵ -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, .epsilon.-caprolactone and isomers thereof, δ -valerolactone and isomers thereof, β -butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00246] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcitol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00247] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00248] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents,

viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00249] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00250] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

[00251] In selected embodiments, the invention provides a pharmaceutical composition for injection containing the combination of the PI3K and BTK inhibitors and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00252] The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00253] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

[00254] Sterile injectable solutions are prepared by incorporating the combination of the PI3K and BTK inhibitors in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical Compositions for Topical Delivery

[00255] In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the combination of the PI3K and BTK inhibitors and a pharmaceutical excipient suitable for transdermal delivery.

[00256] Compositions of the present invention can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

[00257] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*, menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00258] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the combination of the PI3K and BTK inhibitors in controlled amounts, either with or without another agent.

[00259] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, *e.g.*, U.S. Patent Nos. 5,023,252; 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Pharmaceutical Compositions for Inhalation

[00260] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Other Pharmaceutical Compositions

[00261] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingstone, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

[00262] Administration of the combination of the PI3K and BTK inhibitors or pharmaceutical composition of these compounds can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (*e.g.*, transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

[00263] The compositions of the invention may also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration may, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds of the invention may slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound of the invention may be administered, for example, by local delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound of the invention is admixed with a matrix. Such a matrix may be a polymeric matrix, and may serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for example, lactone-based polyesters or copolyesters such as polylactide, polycaprolactoneglycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly(ether-ester) copolymers (e.g. PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (e.g., polyhydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices may be nondegrading or may degrade with time, releasing the compound or compounds. The combination of the PI3K and BTK inhibitors may be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds may be applied in a solvent and the solvent may be allowed to evaporate, thus forming a layer of compound onto the stent. Alternatively, the compound may be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the compound diffuses out of the body of the stent to contact the arterial wall. Such stents may be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound of the invention in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent may be removed via an additional brief solvent wash. In yet other embodiments, compounds of the invention may be covalently linked to a stent or graft. A covalent linker may be used which degrades *in vivo*, leading to the release of the compound of the invention. Any bio-labile linkage may be used for such a purpose, such as ester, amide or anhydride linkages. The combination of the PI3K and BTK inhibitors may additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the combination of the PI3K and BTK inhibitors via the pericard or via

advential application of formulations of the invention may also be performed to decrease restenosis.

[00264] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00265] The invention also provides kits. The kits include each of the PI3K and BTK inhibitors, either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. The kit may further contain another agent. In selected embodiments, the PI3K and BTK inhibitors and the agent are provided as separate compositions in separate containers within the kit. In selected embodiments, the PI3K and BTK inhibitors and the agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer.

Dosages and Dosing Regimens

[00266] The amounts of the combination of the PI3K and BTK inhibitors administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human,

this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

[00267] In selected embodiments, the combination of the PI3K and BTK inhibitors is administered in a single dose. Typically, such administration will be by injection - *e.g.*, intravenous injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of the combination of the PI3K and BTK inhibitors may also be used for treatment of an acute condition.

[00268] In selected embodiments, the combination of the PI3K and BTK inhibitors is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In other embodiments, the combination of the PI3K and BTK inhibitors is administered about once per day to about 6 times per day. In another embodiment the administration of the combination of the PI3K and BTK inhibitors continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00269] Administration of the agents of the invention may continue as long as necessary. In selected embodiments, the combination of the PI3K and BTK inhibitors is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the combination of the PI3K and BTK inhibitors is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In selected embodiments, the combination of the PI3K and BTK inhibitors is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects.

[00270] An effective amount of the combination of the PI3K and BTK inhibitors may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Methods of Treatment

[00271] In selected embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PI3K inhibitor (or a PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor) and BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both the PI3K inhibitor (or a PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor) or the BTK inhibitor. In selected embodiments, the method relates to the treatment of cancer such as non-Hodgkin's lymphomas (such as diffuse large B-cell lymphoma), acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, bone (*e.g.*, metastatic bone), esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (*e.g.*, lymphoma and Kaposi's sarcoma), viral-induced cancers, B cell acute lymphoblastic leukemia, Burkitt's leukemia, juvenile myelomonocytic leukemia, hairy cell leukemia, Hogkin's disease, multiple myeloma, mast cell leukemia, or mastocytosis. In selected embodiments, the method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate conditions (*e.g.*, benign prostatic hypertrophy (BPH)).

[00272] In selected embodiments, the invention relates to a method of treating an inflammatory, immune, or autoimmune disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PI3K inhibitor (or a PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor) and BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both the PI3K inhibitor (or a PI3K- γ inhibitor, PI3K- δ inhibitor, or PI3K- γ,δ inhibitor) or the BTK inhibitor. In selected embodiments, the invention also relates to a method of treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma and melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcet's disease,

polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidradenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, Crohn's Disease, lupus, and lupus nephritis.

EXAMPLES

[00273] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

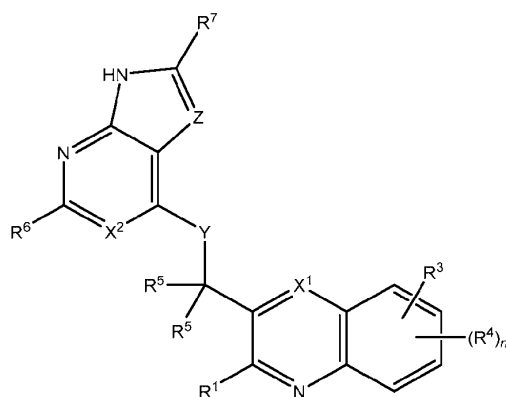
[00274] Ficoll purified mantle cell lymphoma (MCL) cells (2×10^5) isolated from bone marrow or peripheral blood were treated with each drug alone and with six equimolar concentrations of a BTK inhibitor (Formula XVIII) and a PI3K- δ inhibitor (Formula IX) ranging from 0.01 nM to 10 μ M on 96-well plates in triplicate. Plated cells were then cultured in HS-5 conditioned media at 37°C with 5% CO₂. After 72 hours of culture, cell viability was determined using an (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The potential synergy of the combination of the BTK inhibitor of Formula XVIII and the PI3K- δ inhibitor of Formula IX at a given equimolar concentration was determined using the median effect model as described in Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul.* 1984; 22: 27-55. The statistical modeling was run in R using a script that utilizes the median effect model as described in Lee JJ, Kong M, Ayers GD, Lotan R, Interaction index and different methods for determining drug interaction in combination therapy. *J Biopharm Stat.* 2007; 17(3): 461-80. A value of 1, less than 1, and greater than 1 using R defines an additive interaction, synergistic and antagonistic, respectively. The Lee et al. method calculates a 95% confidence interval for each data point. For each viability curve, to be considered synergistic, a data point must have an interaction index below 1 and the upper confidence interval must also be below 1. In order to summarize and demonstrate collective synergy results, an interaction dot blot was generated for the primary patient samples.

[00275] A similar approach was utilized to study diffuse large B cell lymphoma (DLBCL) (TMD8) and MCL (MINO) cell lines. Cells were treated with each drug alone and with six equimolar concentrations of the BTK inhibitor of Formula XVIII and the PI3K- δ inhibitor of Formula IX ranging from 0.003 nM to 1.0 μ M (for TMD8) or 0.03 nM to 10 μ M (for MINO) on 96-well plates in triplicate. Plated cells were then cultured in standard conditioned media plus FBS at 37°C with 5% CO₂. After 72 hours of culture, viability was determined using an MTS assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The results of the experiments described in this example are shown in FIGS 1, 2, 3, and 4.

[00276] The following numbered paragraphs 1-24 describe further embodiments of the invention, which are provided by way of example only and are not intended to otherwise limit the scope of the invention.

1. A method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor and a Bruton's tyrosine kinase (BTK) inhibitor.
2. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K- γ inhibitor.
3. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K- δ inhibitor.
4. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K- γ,δ inhibitor.
5. The method of paragraph 1, wherein the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers.
6. The method of paragraph 1, wherein the combination of the PI3K inhibitor with the BTK inhibitor is administered by intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.
7. The method of paragraph 1, wherein the PI3K inhibitor or BTK inhibitor is in the form of a pharmaceutically acceptable salt.

8. The method of paragraph 1, wherein the PI3K inhibitor is administered to the subject before administration of the BTK inhibitor.
9. The method of paragraph 1, wherein the PI3K inhibitor is administered concurrently with the administration of the BTK inhibitor.
10. The method of paragraph 1, wherein the PI3K inhibitor is administered to the subject after administration of the BTK inhibitor.
11. The method of paragraph 1, wherein the PI3K inhibitor is:



or any pharmaceutically-acceptable salt thereof, wherein:

X¹ is C(R⁹) or N;

X² is C(R₁₀) or N;

Y is N(R¹¹), O or S;

Z is CR⁸ or N;

n is 0, 1, 2 or 3;

R¹ is a direct-bonded or oxygen-linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄alkyl, OC₁₋₄alkyl, OC₁₋₄haloalkyl, NHC₁₋₄, N(C₁₋₄alkyl)C₁₋₄alkyl and C₁₋₄haloalkyl;

R^2 is selected from halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $OS(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^2 is selected from $C_{1-6}alkyl$, phenyl, benzyl, heteroaryl, heterocycle, $-(C_{1-3}alkyl)heteroaryl$, $-(C_{1-3}alkyl)heterocycle$, $-O(C_{1-3}alkyl)heteroaryl$, $-O(C_{1-3}alkyl)heterocycle$, $-NR^a(C_{1-3}alkyl)heteroaryl$, $-NR^a(C_{1-3}alkyl)heterocycle$, $-(C_{1-3}alkyl)phenyl$, $-O(C_{1-3}alkyl)phenyl$ and $-NR^a(C_{1-3}alkyl)phenyl$ all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4} haloalkyl, $OC_{1-4}alkyl$, Br, Cl, F, I and $C_{1-4}alkyl$;

R^3 is selected from H, halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^2$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $C_{1-6}alkyl$, phenyl, benzyl, heteroaryl and heterocycle, wherein the $C_{1-6}alkyl$, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} haloalkyl, $OC_{1-6}alkyl$, Br, Cl, F, I and $C_{1-6}alkyl$;

R^4 is, independently, in each instance, halo, nitro, cyano, $C_{1-4}alkyl$, $OC_{1-4}alkyl$, $OC_{1-4}haloalkyl$, $NHC_{1-4}alkyl$, $N(C_{1-4}alkyl)C_{1-4}alkyl$ or $C_{1-4}haloalkyl$;

R^5 is, independently, in each instance, H, halo, $C_{1-6}alkyl$, $C_{1-4}haloalkyl$, or $C_{1-6}alkyl$ substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, $OC_{1-4}alkyl$, $C_{1-4}alkyl$, $C_{1-3}haloalkyl$, $OC_{1-4}alkyl$, NH_2 , $NHC_{1-4}alkyl$, $N(C_{1-4}alkyl)C_{1-4}alkyl$; or both R^5 groups together form a C_{3-6} spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, $OC_{1-4}alkyl$, $C_{1-4}alkyl$, $C_{1-3}haloalkyl$, $OC_{1-4}alkyl$, NH_2 , $NHC_{1-4}alkyl$, $N(C_{1-4}alkyl)C_{1-4}alkyl$;

R^6 is selected from H, halo, $C_{1-6}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$;

R^7 is selected from H, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$;

R^8 is selected from H, C_{1-6} haloalkyl, Br, Cl, F, I, OR^a , NR^aR^a , C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} haloalkyl, OC_{1-6} alkyl, Br, Cl, F, I and C_{1-6} alkyl;

R^9 is selected from H, halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^aC(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, NR^aR^a , $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{1-6}alkyl$, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, NR^aR^a , $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4} haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-$

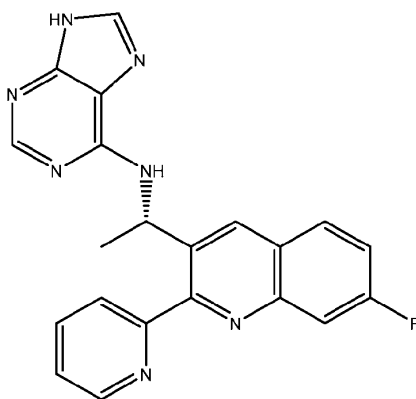
$N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^{10} is H, $C_{1-3}alkyl$, $C_{1-3}haloalkyl$, cyano, nitro, CO_2R^a , $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

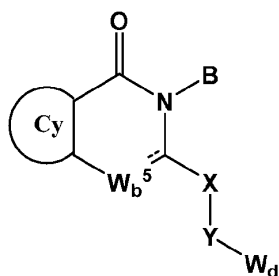
R^{11} is H or $C_{1-4}alkyl$;

R^a is independently, at each instance, H or R^b ; and R^b is independently, at each instance, phenyl, benzyl or $C_{1-6}alkyl$, the phenyl, benzyl and $C_{1-6}alkyl$ being substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}alkyl$, $C_{1-3}haloalkyl$, $-OC_{1-4}alkyl$, $-NH_2$, $-NHC_{1-4}alkyl$, $-N(C_{1-4}alkyl)C_{1-4}alkyl$.

12. The method of paragraph 1, wherein the PI3K inhibitor is:



13. The method of paragraph 1, wherein the PI3K inhibitor is:



or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt thereof, wherein

Cy is aryl or heteroaryl substituted by 0 or 1 occurrence of R^3 and 0, 1, 2, or 3 occurrence(s) of R^5 ;

W_b^5 is CR^8 , CHR^8 , or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl or nitro; B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, 3, or 4 occurrence(s) of R^2 ;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, or carbonate;

X is $-(CH(R^9))_z-$;

Y is $-N(R^9)-C(=O)-$, $-C(=O)-N(R^9)-$, $-C(=O)-N(R^9)-(CHR^9)-$, $-N(R^9)-S(=O)-$, $-S(=O)-N(R^9)-$, $-S(=O)_2-N(R^9)-$, $-N(R^9)-C(=O)-N(R^9)$ or $-N(R^9)S(=O)_2-$;

z is an integer of 1, 2, 3, or 4;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro;

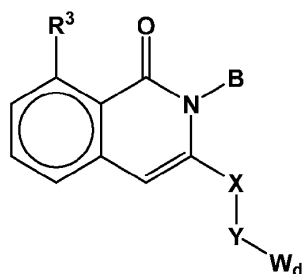
each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or heteroalkyl; or two adjacent occurrences of R^9 together with the atoms to which they are attached form a 4- to 7-membered ring;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl, each of which is substituted with one or more R^{10} , R^{11} , R^{12} or R^{13} , and

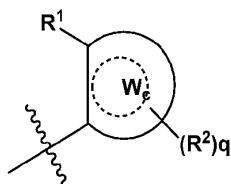
R^{10} , R^{11} , R^{12} and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate or $NR'R''$ wherein R' and R'' are taken together with nitrogen to form a cyclic moiety.

14. The method of paragraph 14, wherein the PI3K inhibitor is:



or its pharmaceutically acceptable salt thereof, wherein

B is:



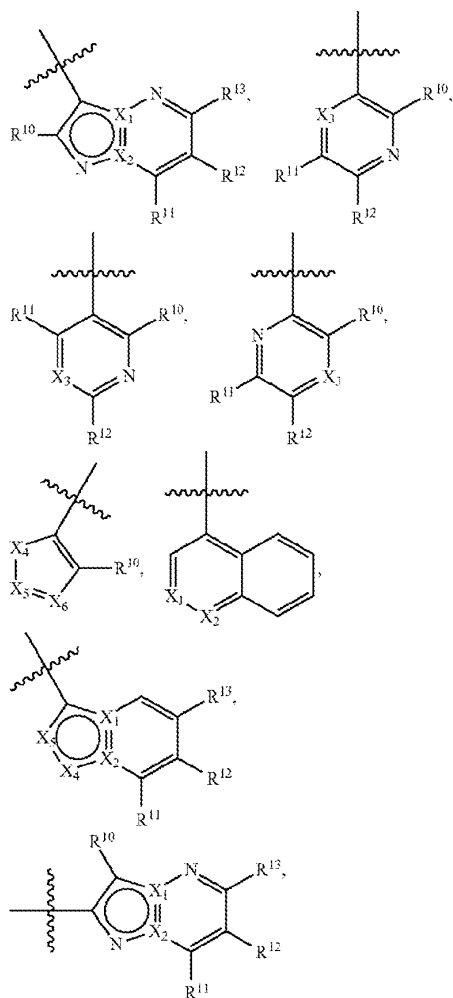
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

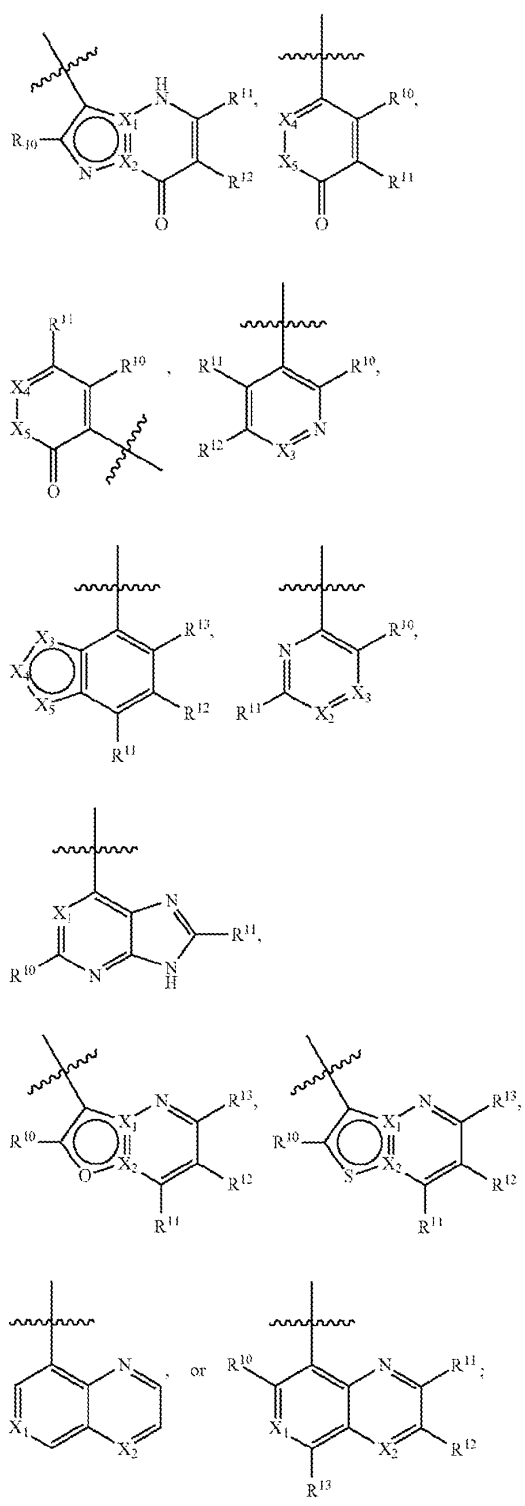
q is an integer of 0, 1, 2, 3, or 4;

X is a bond or $-(CH(R^9))_z-$, and z is an integer of 1;

Y is $-N(R^9)-$;

W_d is:





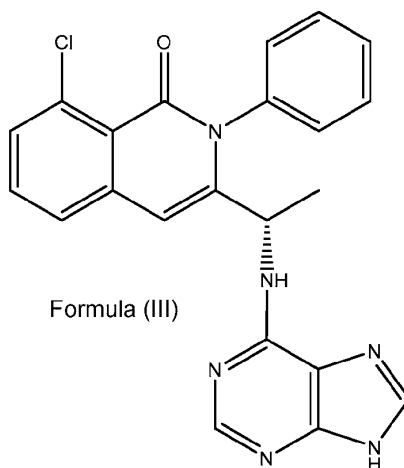
X₁, X₂ and X₃ are each independently C, CR¹³ or N; and X₄, X₅ and X₆ are each independently N, NH, CR¹³, S or O;

R¹ is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxy carbonyl, sulfonamido, halo, cyano, or nitro;

R² is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; R³ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxy carbonyl sulfonamido, halo, cyano, hydroxy or nitro; and

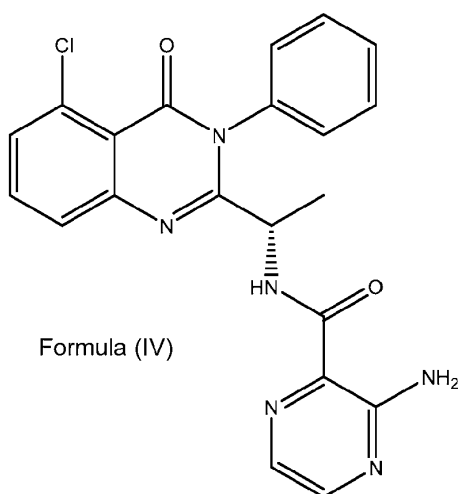
each instance of R⁹ is independently hydrogen, alkyl, or heterocycloalkyl.

15. The method of paragraph 14, wherein the PI3K inhibitor is



or a pharmaceutically acceptable salt thereof.

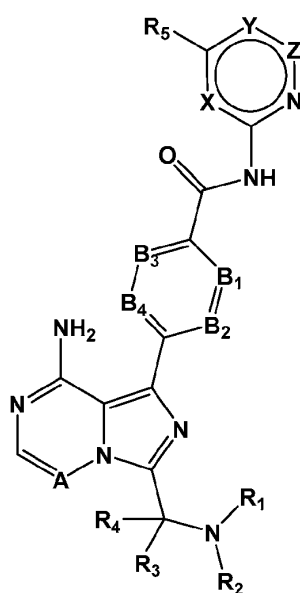
16. The method of paragraph 14, wherein the PI3K inhibitor is



Formula (IV)

or a pharmaceutically acceptable salt thereof.

17. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

X is CH, N, O or S;

Y is C(R₆), N, O or S;

Z is CH, N or bond;

A is CH or N;

B₁ is N or C(R₇);

B₂ is N or C(R₈);

B₃ is N or C(R₉);

B₄ is N or C(R₁₀);

R₁ is R₁₁C(O), R₁₂S(O), R₁₃SO₂ or (1-6C)alkyl optionally substituted with R₁₄;

R₂ is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R₃ is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R₂ and R₃ form, together with the N and C atom they are attached to, a (3- 7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R₄ is H or (1-3C)alkyl;

R₅ is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R₅ is (6-10C)aryl or (2-6C)heterocycloalkyl;

R₆ is H or (1-3C)alkyl; or

R₅ and R₆ together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R₇ is H, halogen, CF₃, (1-3C)alkyl or (1-3C)alkoxy;

R₈ is H, halogen, CF₃, (1-3C)alkyl or (1-3C)alkoxy; or

R₇ and R₈ together with the carbon atoms they are attached to, form (6-10C)aryl or (1-9C)heteroaryl;

R₉ is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R₁₀ is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R₁₁ is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or R₁₁ is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

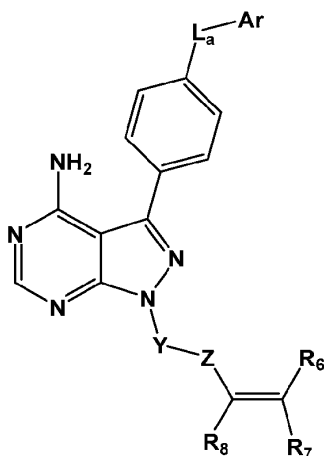
R₁₁ is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R₁₂ and R₁₃ are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano; and

R₁₄ is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl.

18. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

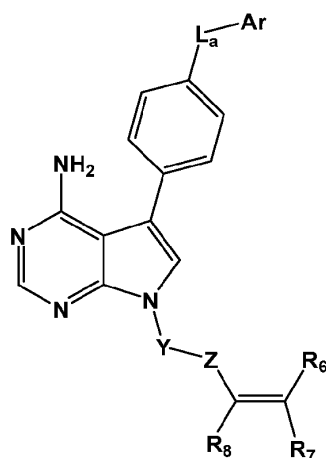
Z is $C(=O)$, $OC(=O)$, $NRC(=O)$, $C(=S)$, $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1 - C_6 alkyl.

19. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

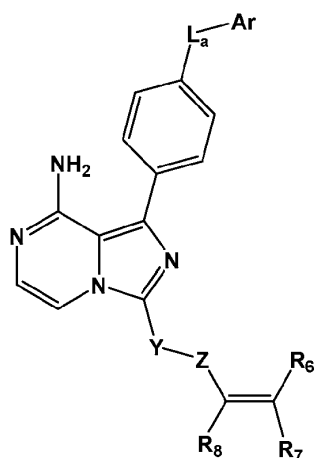
Z is $C(=O)$, $OC(=O)$, $NRC(=O)$, $C(=S)$, $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1 - C_6 alkyl.

20. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

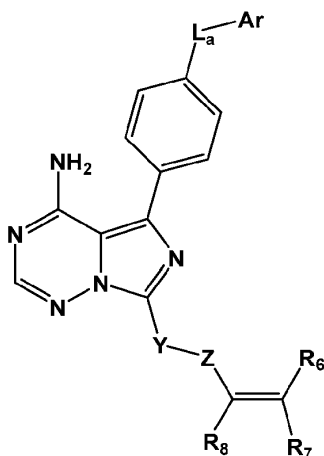
Z is $C(=O)$, $OC(=O)$, $NRC(=O)$, $C(=S)$, $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1 - C_6 alkyl.

21. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

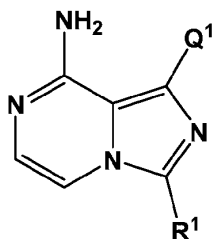
Z is $C(=O)$, $OC(=O)$, $NRC(=O)$, $C(=S)$, $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1 - C_6 alkyl.

22. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is aryl¹, heteroaryl¹, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one to five independent G^1 substituents;

R^1 is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, or heterobicycloalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

G^1 and G^{41} are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, $-CN$, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C=O)R^3$, $NR^2(C=O)OR^3$, $NR^2(C=O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C=S)OR^2$, $-(C=O)SR^2$, $-NR^2(C=NR^3)NR^{2a}R^{3a}$, $-NR^2(C=NR^3)OR^{2a}$, $-NR^2(C=NR^3)SR^{3a}$, $-O(C=O)OR^2$, $-O(C=O)NR^2R^3$, $-O(C=O)SR^2$, $-S(C=O)OR^2$, $-S(C=O)NR^2R^3$, $C_{0-10}alkyl$, $C_{2-10}alkenyl$, $C_{2-10}alkynyl$, $C_{1-10}alkoxyC_{1-10}alkyl$, $C_{1-10}alkoxyC_{2-10}alkenyl$, $C_{1-10}alkoxyC_{2-10}alkynyl$, $C_{1-10}alkylthioC_{1-10}alkyl$, $C_{1-10}alkylthioC_{2-10}alkenyl$, $C_{1-10}alkylthioC_{2-10}alkynyl$, $cycloC_{3-8}alkyl$, $cycloC_{3-8}alkenyl$, $cycloC_{3-8}alkylC_{1-10}alkyl$, $cycloC_{3-8}alkenylC_{1-10}alkyl$, $cycloC_{3-8}alkylC_{2-10}alkenyl$, $cycloC_{3-8}alkenylC_{2-10}alkenyl$, $cycloC_{3-8}alkylC_{2-10}alkynyl$, $cycloC_{3-8}alkenylC_{2-10}alkynyl$, $heterocyclyl-C_{0-10}alkyl$, $heterocyclyl-C_{2-10}alkenyl$, or $heterocyclyl-C_{2-10}alkynyl$, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or $-(X^1)_n$ $(Y^1)_m-R^4$; or aryl- $C_{0-10}alkyl$, aryl- $C_{2-10}alkenyl$, or aryl- $C_{2-10}alkynyl$, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or hetaryl- $C_{0-10}alkyl$, hetaryl- $C_{2-10}alkenyl$, or hetaryl- $C_{2-10}alkynyl$, any of which is optionally

substituted with one or more independent halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{222}$, $-\text{NR}^{222}$, $\text{R}^{333}(\text{R}^{333a})_{j3a}$, $-\text{C}(\text{O})\text{R}^{222}$, $-\text{CO}_2\text{R}^{222}$, $-\text{CONR}^{222}\text{R}^{333}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_{j3a}\text{R}^{222}$, $-\text{SO}_2\text{NR}^{222}\text{R}^{333}$, $\text{NR}^{222}(\text{C}=\text{O})\text{R}^{333}$, $\text{NR}^{222}(\text{C}=\text{O})\text{OR}^{333}$, $\text{NR}^{222}(\text{C}=\text{O})\text{NR}^{222}\text{R}^{333}$, $\text{NR}^{222}\text{S}(\text{O})_{j3a}\text{R}^{333}$, $-(\text{C}=\text{S})\text{OR}^{222}$, $-(\text{C}=\text{O})\text{SR}^{222}$, $-\text{NR}^{222}(\text{C}=\text{NR}^{333})\text{NR}^{222a}\text{R}^{333a}$, $-\text{NR}^{222}(\text{C}=\text{NR}^{333})\text{OR}^{222a}$, $-\text{NR}^{222}(\text{C}=\text{NR}^{333})\text{SR}^{333a}$, $-\text{O}(\text{C}=\text{O})\text{OR}^{222}$, $-\text{O}(\text{C}=\text{O})\text{NR}^{222}\text{R}^{333}$, $-\text{O}(\text{C}=\text{O})\text{SR}^{222}$, $-\text{S}(\text{C}=\text{O})\text{OR}^{222}$, or $-\text{S}(\text{C}=\text{O})\text{NR}^{222}\text{R}^{333}$ substituents;

G^{11} is halo, oxo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{31}(\text{R}^{3a1})_{j4}$, $-\text{C}(\text{O})\text{R}^{21}$, $-\text{CO}_2\text{R}^{21}$, $-\text{CONR}^{21}\text{R}^{31}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_{j4}\text{R}^{21}$, $-\text{SO}_2\text{NR}^{21}\text{R}^{31}$, $\text{NR}^{21}(\text{C}=\text{O})\text{R}^{31}$, $\text{NR}^{21}(\text{C}=\text{O})\text{OR}^{31}$, $\text{NR}^{21}(\text{C}=\text{O})\text{NR}^{21}\text{R}^{31}$, $\text{NR}^{21}\text{S}(\text{O})_{j4}\text{R}^{31}$, $-(\text{C}=\text{S})\text{OR}^{21}$, $-(\text{C}=\text{O})\text{SR}^{21}$, $-\text{NR}^{21}(\text{C}=\text{NR}^{31})\text{NR}^{2a1}\text{R}^{3a1}$, $-\text{NR}^{21}(\text{C}=\text{NR}^{31})\text{OR}^{2a1}$, $-\text{NR}^{21}(\text{C}=\text{NR}^{31})\text{SR}^{3a1}$, $-\text{O}(\text{C}=\text{O})\text{OR}^{21}$, $-\text{O}(\text{C}=\text{O})\text{NR}^{21}\text{R}^{31}$, $-\text{O}(\text{C}=\text{O})\text{SR}^{21}$, $-\text{S}(\text{C}=\text{O})\text{OR}^{21}$, $-\text{S}(\text{C}=\text{O})\text{NR}^{21}\text{R}^{31}$, $-\text{P}(\text{O})\text{OR}^{21}\text{OR}^{31}$, $\text{C}_{0-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{C}_{1-10}\text{alkoxyC}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkoxyC}_{2-10}\text{alkenyl}$, $\text{C}_{1-10}\text{alkoxyC}_{2-10}\text{alkynyl}$, $\text{C}_{1-10}\text{alkylthioC}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkylthioC}_{2-10}\text{alkenyl}$, $\text{C}_{1-10}\text{alkylthioC}_{2-10}\text{alkynyl}$, $\text{cycloC}_3\text{-8alkyl}$, $\text{cycloC}_3\text{-8alkenyl}$, $\text{cycloC}_3\text{-8alkylC}_{1-10}\text{alkyl}$, $\text{cycloC}_3\text{-8alkenylC}_{1-10}\text{alkyl}$, $\text{cycloC}_3\text{-8alkylC}_{2-10}\text{alkenyl}$, $\text{cycloC}_3\text{-8alkenylC}_{2-10}\text{alkenyl}$, $\text{cycloC}_3\text{-8alkylC}_{2-10}\text{alkynyl}$, $\text{cycloC}_3\text{-8alkenylC}_{2-10}\text{alkynyl}$, $\text{heterocyclyl-C}_{0-10}\text{alkyl}$, $\text{heterocyclyl-C}_{2-10}\text{alkenyl}$, or $\text{heterocyclyl-C}_{2-10}\text{alkynyl}$, any of which is optionally substituted with one or more independent halo, oxo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{2221}$, $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{333a1})_{j4a}$, $-\text{C}(\text{O})\text{R}^{2221}$, $-\text{CO}_2\text{R}^{2221}$, $-\text{CONR}^{2221}\text{R}^{3331}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_{j4a}\text{R}^{2221}$, $-\text{SO}_2\text{NR}^{2221}\text{R}^{3331}$, $\text{NR}^{2221}(\text{C}=\text{O})\text{R}^{3331}$, $\text{NR}^{2221}(\text{C}=\text{O})\text{OR}^{3331}$, $\text{NR}^{2221}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$, $\text{NR}^{2221}\text{S}(\text{O})_{j4a}\text{R}^{3331}$, $-(\text{C}=\text{S})\text{OR}^{2221}$, $-(\text{C}=\text{O})\text{SR}^{2221}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{NR}^{222a1}\text{R}^{333a1}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{OR}^{222a1}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{SR}^{333a1}$, $-\text{O}(\text{C}=\text{O})\text{OR}^{2221}$, $-\text{O}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$, $-\text{O}(\text{C}=\text{O})\text{SR}^{2221}$, $-\text{S}(\text{C}=\text{O})\text{OR}^{2221}$, $-\text{P}(\text{O})\text{OR}^{2221}\text{OR}^{3331}$, or $-\text{S}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$ substituents; or $\text{aryl-C}_{0-10}\text{alkyl}$, $\text{aryl-C}_{2-10}\text{alkenyl}$, or $\text{aryl-C}_{2-10}\text{alkynyl}$, any of which is optionally substituted with one or more independent halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{2221}$, $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{333a1})_{j5a}$, $-\text{C}(\text{O})\text{R}^{2221}$, $-\text{CO}_2\text{R}^{2221}$, $-\text{CONR}^{2221}\text{R}^{3331}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_{j5a}\text{R}^{2221}$, $-\text{SO}_2\text{NR}^{2221}\text{R}^{3331}$, $\text{NR}^{2221}(\text{C}=\text{O})\text{R}^{3331}$, $\text{NR}^{2221}(\text{C}=\text{O})\text{OR}^{3331}$, $\text{NR}^{2221}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$, $\text{NR}^{2221}\text{S}(\text{O})_{j5a}\text{R}^{3331}$, $-(\text{C}=\text{S})\text{OR}^{2221}$, $-(\text{C}=\text{O})\text{SR}^{2221}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{NR}^{222a1}\text{R}^{333a1}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{OR}^{222a1}$, $-\text{NR}^{2221}(\text{C}=\text{NR}^{3331})\text{SR}^{333a1}$, $-\text{O}(\text{C}=\text{O})\text{OR}^{2221}$, $-\text{O}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$, $-\text{O}(\text{C}=\text{O})\text{SR}^{2221}$, $-\text{S}(\text{C}=\text{O})\text{OR}^{2221}$, $-\text{P}(\text{O})\text{OR}^{2221}\text{R}^{3331}$, or $-\text{S}(\text{C}=\text{O})\text{NR}^{2221}\text{R}^{3331}$ substituents; or $\text{hetaryl-C}_{0-10}\text{alkyl}$, $\text{hetaryl-C}_{2-10}\text{alkenyl}$, or $\text{hetaryl-C}_{2-10}\text{alkynyl}$, any of which is optionally substituted with one or more independent halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{2221}$, $-\text{NR}^{2221}\text{R}^{3331}(\text{R}^{333a1})_{j6a}$, $-\text{C}(\text{O})\text{R}^{2221}$, $-\text{CO}_2\text{R}^{2221}$, $-\text{CONR}^{2221}\text{R}^{3331}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{S}(\text{O})_{j6a}\text{R}^{2221}$, $-\text{SO}_2\text{NR}^{2221}\text{R}^{3331}$,

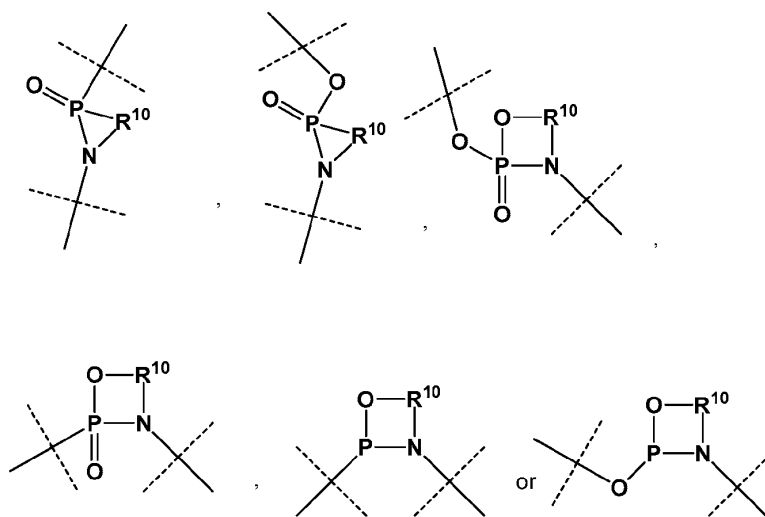
NR²²²¹(C=O)R³³³¹, NR²²²¹(C=O)OR³³³¹, NR²²²¹(C=O)NR²²²¹R³³³¹, NR²²²¹S(O)_{j6a}R³³³¹,
 -(C=S)OR²²²¹, -(C=O)SR²²²¹, -NR²²²¹(C=NR³³³¹)NR^{222a1}R^{333a1}, -NR²²²¹(C=NR³³³¹)OR^{222a1},
 -NR²²²¹(C=NR³³³¹)SR^{333a1}, -O(C=O)OR²²²¹, -O(C=O)NR²²²¹R³³³¹, -O(C=O)SR²²²¹,
 -S(C=O)OR²²²¹, -P(O)OR²²²¹OR³³³¹, or -S(C=O)NR²²²¹R³³³¹ substituents; or G¹¹ is taken
 together with the carbon to which it is attached to form a double bond which is substituted with
 R⁵ and G¹¹¹;

R², R^{2a}, R³, R^{3a}, R²²², R^{222a}, R³³³, R^{333a}, R²¹, R^{2a1}, R³¹, R^{3a1}, R²²²¹, R^{222a1}, R³³³¹, and R^{333a1} are
 each independently equal to C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀
 alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋₁₀alkynyl, C₁₋₁₀alkylthioC₁₋₁₀alkyl, C₁₋₁₀alkylthioC₂₋₁₀
 alkenyl, C₁₋₁₀alkylthioC₂₋₁₀alkynyl, cycloC₃₋₈alkyl, cycloC₃₋₈alkenyl, cycloC₃₋₈alkylC₁₋₁₀alkyl,
 cycloC₃₋₈alkenylC₁₋₁₀alkyl, cycloC₃₋₈alkylC₂₋₁₀alkenyl, cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈
 alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀
 alkenyl, or heterocyclyl-C₂₋₁₀alkynyl, any of which is optionally substituted by one or more
 G¹¹¹ substituents; or aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, or aryl-C₂₋₁₀alkynyl, hetaryl-C₀₋₁₀alkyl,
 hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted by one or
 more G¹¹¹ substituents; or in the case of -NR²R³(R^{3a})_{j1} or -NR²²²R³³³(R^{333a})_{j1a} or
 -NR²²²R³³³(R^{333a})_{j2a} or -NR²²²¹R³³³¹(R^{333a1})_{j3a} or -NR²²²¹R³³³¹(R^{333a1})_{j4a} or -NR²²²¹R³³³¹(R^{333a1})_{j5a}
 or -NR²²²¹R³³³¹(R^{333a1})_{j6a}, R² and R³ or R²²² and R³³³ or R²²²¹ and R³³³¹ taken together with the
 nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring,
 heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally
 substituted by one or more G¹¹¹ substituents;

X¹ and Y¹ are each independently -O-, -NR⁷-, -S(O)_{j7}-, -CR⁵R⁶-, -N(C(O)OR⁷)-, -N(C(O)R⁷)-,
 -N(SO₂R⁷)-, -CH₂O-, -CH₂S-, -CH₂N(R⁷)-, -CH(NR⁷)-, -CH₂N(C(O)R⁷)-, -CH₂N(C(O)OR⁷)-,
 -CH₂N(SO₂R⁷)-, -CH(NHR⁷)-, -CH(NHC(O)R⁷)-, -CH(NHSO₂R⁷)-, -CH(NHC(O)OR⁷)-,
 -CH(OC(O)R⁷)-, -CH(OC(O)NHR⁷)-, -CH=CH-, -C.ident.C-, -C(=NOR⁷)-, -C(O)-, -CH(OR⁷)-,
 -C(O)N(R⁷)-, -N(R⁷)C(O)-, -N(R⁷)S(O)-, -N(R⁷)S(O)₂-, -OC(O)N(R⁷)-, -N(R⁷)C(O)N(R⁷)-,
 -NR⁷C(O)O-, -S(O)N(R⁷)-, -S(O)₂N(R⁷)-, -N(C(O)R⁷)S(O)-, -N(C(O)R⁷)S(O)₂-,
 -N(R⁷)S(O)N(R⁷)-, -N(R⁷)S(O)₂N(R⁷)-, -C(O)N(R⁷)C(O)-, -S(O)N(R⁷)C(O)-, -S(O)₂N(R⁷)C(O)-,
 -OS(O)N(R⁷)-, -OS(O)₂N(R⁷)-, -N(R⁷)S(O)O-, -N(R⁷)S(O)₂O-, -N(R⁷)S(O)C(O)-,
 -N(R⁷)S(O)₂C(O)-, -SON(C(O)R⁷)-, -SO₂N(C(O)R⁷)-, -N(R⁷)SON(R⁷)-, -N(R⁷)SO₂N(R⁷)-,

-C(O)O-, -N(R⁷)P(OR⁸)O-, -N(R⁷)P(OR⁸)-, -N(R⁷)P(O)(OR⁸)O-, -N(R⁷)P(O)(OR⁸)-,
 -N(C(O)R⁷)P(OR⁸)O-, -N(C(O)R⁷)P(OR⁸)-, -N(C(O)R⁷)P(O)(OR⁸)O-, -N(C(O)R⁷)P(OR⁸)-,
 -CH(R⁷)S(O)-, -CH(R⁷)S(O)₂-, -CH(R⁷)N(C(O)OR⁷)-, -CH(R⁷)N(C(O)R⁷)-, -CH(R⁷)N(SO₂R⁷)-,
 -CH(R⁷)O-, -CH(R⁷)S-, -CH(R⁷)N(R⁷)-, -CH(R⁷)N(C(O)R⁷)-, -CH(R⁷)N(C(O)OR⁷)-,
 -CH(R⁷)N(SO₂R⁷)-, -CH(R⁷)C(=NOR⁷)-, -CH(R⁷)C(O)-, -CH(R⁷)CH(OR⁷)-,
 -CH(R⁷)C(O)N(R⁷)-, -CH(R⁷)N(R⁷)C(O)-, -CH(R⁷)N(R⁷)S(O)-, -CH(R⁷)N(R⁷)S(O)₂-,
 -CH(R⁷)OC(O)N(R⁷)-, -CH(R⁷)N(R⁷)C(O)N(R⁷)-, -CH(R⁷)NR⁷C(O)O-, -CH(R⁷)S(O)N(R⁷)-,
 -CH(R⁷)S(O)₂N(R⁷)-, -CH(R⁷)N(C(O)R⁷)S(O)-, -CH(R⁷)N(C(O)R⁷)S(O)-,
 -CH(R⁷)N(R⁷)S(O)N(R⁷)-, -CH(R⁷)N(R⁷)S(O)₂N(R⁷)-, -CH(R⁷)C(O)N(R⁷)C(O)-,
 -CH(R⁷)S(O)N(R⁷)C(O)-, -CH(R⁷)S(O)₂N(R⁷)C(O)-, -CH(R⁷)OS(O)N(R⁷)-,
 -CH(R⁷)OS(O)₂N(R⁷)-, -CH(R⁷)N(R⁷)S(O)O-, -CH(R⁷)N(R⁷)S(O)₂O-, -CH(R⁷)N(R⁷)S(O)C(O)-,
 -CH(R⁷)N(R⁷)S(O)₂C(O)-, -CH(R⁷)SON(C(O)R⁷)-, -CH(R⁷)SO₂N(C(O)R⁷)-,
 -CH(R⁷)N(R⁷)SON(R⁷)-, -CH(R⁷)N(R⁷)SO₂N(R⁷)-, -CH(R⁷)C(O)O-, -CH(R⁷)N(R⁷)P(OR⁸)O-,
 -CH(R⁷)N(R⁷)P(OR⁸)-, -CH(R⁷)N(R⁷)P(O)(OR⁸)O-, -CH(R⁷)N(R⁷)P(O)(OR⁸)-,
 -CH(R⁷)N(C(O)R⁷)P(OR⁸)O-, -CH(R⁷)N(C(O)R⁷)P(OR⁸)-, -CH(R⁷)N(C(O)R⁷)P(O)(OR⁸)O-, or
 -CH(R⁷)N(C(O)R⁷)P(OR⁸)-; or

X¹ and Y¹ are each independently represented by one of the following structural formulas:



R¹⁰, taken together with the phosphinamide or phosphonamide, is a 5-, 6-, or 7-membered aryl, heteroaryl or heterocyclyl ring system;

R⁵, R⁶, and G¹¹¹ are each independently a C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋₁₀alkynyl, C₁₋₁₀alkylthioC₁₋₁₀alkyl, C₁₋₁₀alkylthioC₂₋₁₀alkenyl, C₁₋₁₀alkylthioC₂₋₁₀alkynyl, cycloC₃₋₈alkyl, cycloC₃₋₈alkenyl, cycloC₃₋₈alkylC₁₋₁₀alkyl, cycloC₃₋₈alkenylC₁₋₁₀alkyl, cycloC₃₋₈alkylC₂₋₁₀alkenyl, cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, or heterocyclyl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR⁷⁷, -NR⁷⁷R⁸⁷, -C(O)R⁷⁷, -CO₂R⁷⁷, -CONR⁷⁷R⁸⁷, -NO₂, -CN, -S(O)_{j5a}R⁷⁷, -SO₂NR⁷⁷R⁸⁷, NR⁷⁷(C=O)R⁸⁷, NR⁷⁷(C=O)OR⁸⁷, NR⁷⁷(C=O)NR⁷⁸R⁸⁷, NR⁷⁷S(O)_{j5a}R⁸⁷, -(C=S)OR⁷⁷, -(C=O)SR⁷⁷, -NR⁷⁷(C=NR⁸⁷)NR⁷⁸R⁸⁸, -NR⁷⁷(C=NR⁸⁷)OR⁷⁸, -NR⁷⁷(C=NR⁸⁷)SR⁷⁸, -O(C=O)OR⁷⁷, -O(C=O)NR⁷⁷R⁸⁷, -O(C=O)SR⁷⁷, -S(C=O)OR⁷⁷, -P(O)OR⁷⁷OR⁸⁷, or -S(C=O)NR⁷⁷R⁸⁷ substituents; or aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, or aryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR⁷⁷, -NR⁷⁷R⁸⁷, -C(O)R⁷⁷, -CO₂R⁷⁷, -CONR⁷⁷R⁸⁷, -NO₂, -CN, -S(O)_{j5a}R⁷⁷, -SO₂NR⁷⁷R⁸⁷, NR⁷⁷(C=O)R⁸⁷, NR⁷⁷(C=O)OR⁸⁷, NR⁷⁷(C=O)NR⁷⁸R⁸⁷, NR⁷⁷S(O)_{j5a}R⁸⁷, -(C=S)OR⁷⁷, -(C=O)SR⁷⁷, -NR⁷⁷(C=NR⁸⁷)NR⁷⁸R⁸⁸, -NR⁷⁷(C=NR⁸⁷)OR⁷⁸, -NR⁷⁷(C=NR⁸⁷)SR⁷⁸, -O(C=O)OR⁷⁷, -O(C=O)NR⁷⁷R⁸⁷, -O(C=O)SR⁷⁷, -S(C=O)OR⁷⁷, -P(O)OR⁷⁷R⁸⁷, or -S(C=O)NR⁷⁷R⁸⁷ substituents; or hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, -CF₃, -OCF₃, -OR⁷⁷, -NR⁷⁷R⁸⁷, -C(O)R⁷⁷, -CO₂R⁷⁷, -CONR⁷⁷R⁸⁷, -NO₂, -CN, -S(O)_{j5a}R⁷⁷, -SO₂NR⁷⁷R⁸⁷, NR⁷⁷(C=O)R⁸⁷, NR⁷⁷(C=O)OR⁸⁷, NR⁷⁷(C=O)NR⁷⁸R⁸⁷, NR⁷⁷S(O)_{j5a}R⁸⁷, -(C=S)OR⁷⁷, -(C=O)SR⁷⁷, -NR⁷⁷(C=NR⁸⁷)NR⁷⁸R⁸⁸, -NR⁷⁷(C=NR⁸⁷)OR⁷⁸, -NR⁷⁷(C=NR⁸⁷)SR⁷⁸, -O(C=O)OR⁷⁷, -O(C=O)NR⁷⁷R⁸⁷, -O(C=O)SR⁷⁷, -S(C=O)OR⁷⁷, -P(O)OR⁷⁷OR⁸⁷, or -S(C=O)NR⁷⁷R⁸⁷ substituents; or R⁵ with R⁶ taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R⁶⁹; or R⁵ with R⁶ taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R⁶⁹;

R⁷ and R⁸ are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G¹¹¹ substituents;

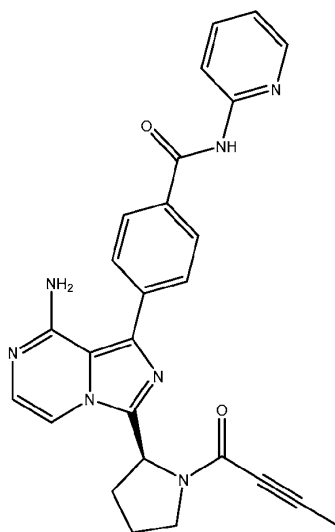
R⁴ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G⁴¹ substituents;

R⁶⁹ is equal to halo, -OR⁷⁸, -SH, -NR⁷⁸R⁸⁸, -CO₂R⁷⁸, -CONR⁷⁸R⁸⁸, -NO₂, -CN, -S(O)_jR⁷⁸, -SO₂NR⁷⁸R⁸⁸, C₀₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxyC₁₋₁₀alkyl, C₁₋₁₀alkoxyC₂₋₁₀alkenyl, C₁₋₁₀alkoxyC₂₋₁₀alkynyl, C₁₋₁₀alkylthioC₁₋₁₀alkyl, C₁₋₁₀alkylthioC₂₋₁₀alkenyl, C₁₋₁₀alkylthioC₂₋₁₀alkynyl, cycloC₃₋₈alkyl, cycloC₃₋₈alkenyl, cycloC₃₋₈alkylC₁₋₁₀alkyl, cycloC₃₋₈alkenylC₁₋₁₀alkyl, cycloC₃₋₈alkylC₂₋₁₀alkenyl, cycloC₃₋₈alkenylC₂₋₁₀alkenyl, cycloC₃₋₈alkylC₂₋₁₀alkynyl, cycloC₃₋₈alkenylC₂₋₁₀alkynyl, heterocyclyl-C₀₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, or heterocyclyl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR⁷⁷⁸, -SO₂NR⁷⁷⁸R⁸⁸⁸, or -NR⁷⁷⁸R⁸⁸⁸ substituents; or aryl-C₀₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, or aryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR⁷⁷⁸, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, haloC₁₋₁₀alkyl, haloC₂₋₁₀alkenyl, haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CONR⁷⁷⁸R⁸⁸⁸, -SO₂NR⁷⁷⁸R⁸⁸⁸, or -NR⁷⁷⁸R⁸⁸⁸ substituents; or hetaryl-C₀₋₁₀alkyl, hetaryl-C₂₋₁₀alkenyl, or hetaryl-C₂₋₁₀alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR⁷⁷⁸, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, haloC₁₋₁₀alkyl, haloC₂₋₁₀alkenyl, haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CONR⁷⁷⁸R⁸⁸⁸, -SO₂NR⁷⁷⁸R⁸⁸⁸, or -NR⁷⁷⁸R⁸⁸⁸ substituents; or mono(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, mono(aryl)aminoC₁₋₆alkyl, di(aryl)aminoC₁₋₆alkyl, or -N(C₁₋₆alkyl)-C₁₋₆alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR⁷⁷⁸, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, haloC₁₋₁₀alkyl, haloC₂₋₁₀alkenyl, haloC₂₋₁₀alkynyl, -COOH, C₁₋₄alkoxycarbonyl, -CONR⁷⁷⁸R⁸⁸⁸, SO₂NR⁷⁷⁸R⁸⁸⁸, or -NR⁷⁷⁸R⁸⁸⁸ substituents; or in the case of -NR⁷⁸R⁸⁸, R⁷⁸ and R⁸⁸ taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C₁₋₁₀alkoxy, -SO₂NR⁷⁷⁸R⁸⁸⁸, or -NR⁷⁷⁸R⁸⁸⁸ substituents;

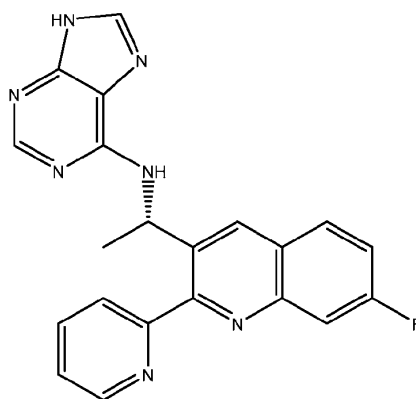
R^{77} , R^{78} , R^{87} , R^{88} , R^{778} , and R^{888} are each independently C_{0-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy C_{1-10} alkyl, C_{1-10} alkoxy C_{2-10} alkenyl, C_{1-10} alkoxy C_{2-10} alkynyl, C_{1-10} alkylthio C_{1-10} alkyl, C_{1-10} alkylthio C_{2-10} alkenyl, C_{1-10} alkylthio C_{2-10} alkynyl, cyclo C_{3-8} alkyl, cyclo C_{3-8} alkenyl, cyclo C_{3-8} alkyl C_{1-10} alkyl, cyclo C_{3-8} alkenyl C_{1-10} alkyl, cyclo C_{3-8} alkyl C_{2-10} alkenyl, cyclo C_{3-8} alkenyl C_{2-10} alkenyl, cyclo C_{3-8} alkyl C_{2-10} alkynyl, cyclo C_{3-8} alkenyl C_{2-10} alkynyl, heterocyclyl- C_{0-10} alkyl, heterocyclyl- C_{2-10} alkenyl, heterocyclyl- C_{2-10} alkynyl, C_{1-10} alkylcarbonyl, C_{2-10} alkenylcarbonyl, C_{2-10} alkynylcarbonyl, C_{1-10} alkoxycarbonyl, C_{1-10} alkoxycarbonyl C_{1-10} alkyl, mono C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C_{1-10} alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10} alkoxy, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; or aryl- C_{0-10} alkyl, aryl- C_{2-10} alkenyl, or aryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O(C_{0-4}alkyl)$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-COOH$, C_{1-4} alkoxycarbonyl, $-CON(C_{0-4}alkyl)(C_{0-10}alkyl)$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; or hetaryl- C_{0-10} alkyl, hetaryl- C_{2-10} alkenyl, or hetaryl- C_{2-10} alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O(C_{0-4}alkyl)$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-COOH$, C_{1-4} alkoxycarbonyl, $-CON(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; or mono(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, mono(aryl)amino C_{1-6} alkyl, di(aryl)amino C_{1-6} alkyl, or $-N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O(C_{0-4}alkyl)$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halo C_{1-10} alkyl, halo C_{2-10} alkenyl, halo C_{2-10} alkynyl, $-COOH$, C_{1-4} alkoxycarbonyl, $-CON(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; and

n, m, j1, j1a, j2a, j3a, j4, j4a, j5a, j6a, j7, and j8 are each independently equal to 0, 1, or 2.

23. The method of paragraphs 1, 2, or 3, wherein the BTK inhibitor is:



or a pharmaceutically-acceptable salt thereof, and the PI3K inhibitor is:



or a pharmaceutically-acceptable salt thereof.

24. The method of paragraphs 1, 2, or 3, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically-acceptable salt thereof, and the PI3K inhibitor or PI3K- δ inhibitor is (*S*)-*N*-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

ABSTRACT

[00277] A therapeutic combination of a phosphoinositide 3-kinase (PI3K) inhibitor, including PI3K inhibitors selective for the γ - and δ -isoforms and selective for both γ - and δ -isoforms, and a Bruton's tyrosine kinase (BTK) inhibitor is described.