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[Continued on next page]

(54) Title: TARGETING PIM KINASES IN COMBINATION WITH BTK INHIBITION

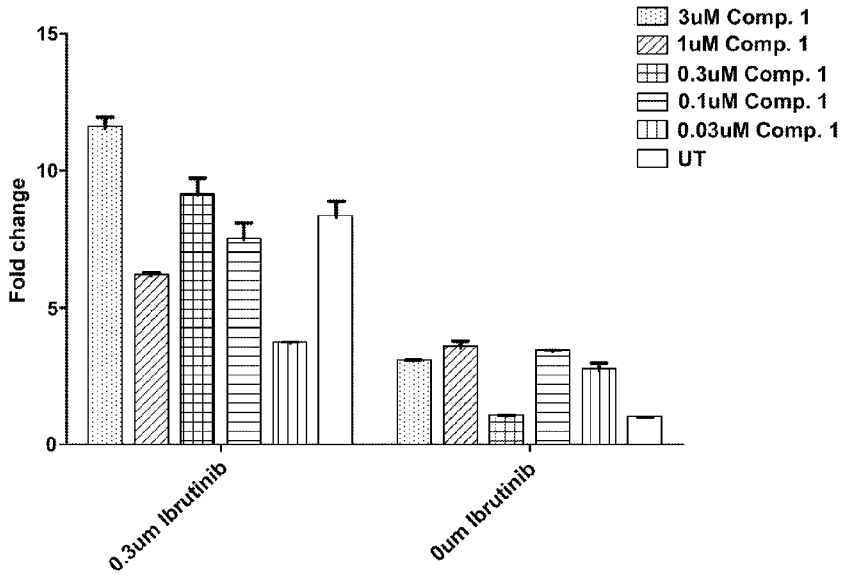

Fig. 11

(57) Abstract: Combination therapies for treatment of cancer are provided. The disclosed methods comprise administration of a PIM kinase inhibitor and a BTK inhibitor to a mammal in need thereof.

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TARGETING PIM KINASES IN COMBINATION WITH BTK INHIBITION

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/142, 354 filed on April 2, 2015, and U.S. Provisional Application No. 62/150,695 filed on April 21, 2015, which applications are incorporated by reference herein in their entirety.

BACKGROUND

Technical Field

The present invention is generally directed to methods for treatment of cancer by administration of a PIM kinase inhibitor in combination with a BTK inhibitor.

Description of the Related Art

BTK inhibitors (*e.g.* ibrutinib) have significantly impacted the treatment of B-cell malignancies in a positive way. Single agent response rates with ibrutinib are 65% or higher in B-cell lymphomas and chronic lymphocytic leukaemia with the majority of patients enjoying a prolonged duration of response. Continued clinical development is needed, however, as most patients achieve only a partial response from their treatment and ultimately patients become refractory to ibrutinib leading to relapse and disease progression. Targeted combinations with ibrutinib could potentially increase the number of patients undergoing complete remission and combat emergent resistant mechanisms.

The PIM family (1, 2, and 3) are serine/threonine kinases that have proven to be oncogenic in-part due to their ability to suppress c-Myc induced apoptosis. Pim-1 kinase is known to be involved in a number of cytokine signaling pathways as a downstream effector. Once activated, Pim-1 kinase causes progression of the cell cycle, inhibition of apoptosis and modulation of other signal transduction pathways, including its own. Pim-1 kinase is also known to effect activation of transcription factors such as NFAT, p100, c-Myb and Pap-1, and inhibition of others such as HP1. Normal expression of Pim-1 kinase is seen in cells of hematopoietic origin, such as fetal liver, thymus, spleen and bone marrow. Additionally, expression is seen in prostate and oral epithelial cells. Pim-1 kinase is believed to be involved in the initiation or progression of malignant transformation leading to malignancies including Burkitt's lymphoma, prostate cancer, oral cancer and diffuse large cell lymphomas, among

others. Accordingly, the PIM kinases have emerged as important regulators of drug resistance in multiple cancer types, such as prostate cancer, AML, and lymphoma.

BTK and PIM kinases are both attractive individual targets for treatment of various cancers; however, targeting of both BTK and PIM kinase in a single patient has yet to be shown. While progress has been made, there remains a need in the art for improved combination therapies for treating cancer. The present invention fulfills this need and provides related advantages.

BRIEF SUMMARY

Embodiments of the present invention are directed to methods for treating cancer by administration of a PIM kinase inhibitor and a BTK inhibitor to a mammal in need thereof. While not wishing to be bound by theory, it is believed that the signaling crosstalk between BTK and PIM through the STAT transcription factors results in synergies through the simultaneous targeting of both kinases. Experiments performed in support of the present invention demonstrate a significant increase in drug activity when a BTK inhibitor, such as ibrutinib, is combined with a PIM kinase inhibitor (*e.g.*, compound 1) in various lymphoma cell lines. In Granta-519 cells, the IC50 of ibrutinib decreased 3.5-fold, from 0.7 mM to 0.2 mM, when cultured in combination with a subtoxic concentration of compound 1 (300 nM). Similarly, the IC50 of compound 1 decreased 6-fold, from 2.4 mM to 0.4 mM, when cells were cultured in combination with a subtoxic concentration of ibrutinib (100 nM). These results provide evidence that inhibitors of PIM and BTK, when used in combination, are highly effective for the treatment of B-cell malignancies and other B-cell mediated diseases.

Accordingly, in one embodiment a method for treating cancer is provided, the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor. Related methods for decreasing expression of c-Myc in mammalian cells are also provided.

In other embodiments, pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient, a PIM kinase inhibitor and a BTK inhibitor are provided.

In still other embodiments, the invention is directed to a kit comprising a PIM kinase inhibitor, a BTK inhibitor and instructions for administering the PIM kinase inhibitor and BTK inhibitor to a mammal in need thereof.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein

which describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

In the figures, identical reference numbers identify similar elements. The sizes and relative positions of elements in the figures are not necessarily drawn to scale and some of these elements are arbitrarily enlarged and positioned to improve figure legibility. Further, the particular shapes of the elements as drawn are not intended to convey any information regarding the actual shape of the particular elements, and have been solely selected for ease of recognition in the figures.

Fig. 1 is a diagram illustrating the signaling crosstalk between BTK and PIM through the STAT transcription factors.

Fig. 2 is IC50 data for compound 1 against a variety of cell lines and types.

Figs 3A and 3B show IC50 data for inhibition of PIM1 (3A) and PIM3 (3B) with compound 1.

Fig. 4 is an IC50 curve for PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ activity upon treatment with compound 1. Control compound was tested in 10-dose IC50 mode with 3-fold serial dilution starting at 20 μM.

Fig. 5 is MSD data showing decrease in Phospho(Ser473)/Total Akt. PC3 cells were treated with compound 1 for 24 hours.

Figs. 6A and 6B present western blot gel data (6A) and quantitative results (6B) for inhibition of c-Myc in Granta-4 cells by compound 1 acting as a single agent.

Figs. 7A and 7B provide single agent cell viability data for compound 1 and ibrutinib, respectively.

Figs. 8A and 8B are IC50 curves for Grant-519 cells treated with subtoxic doses of ibrutinib and varying concentrations of compound 1 (8A) or subtoxic doses of compound 1 and varying concentrations of compound ibrutinib.

Figure 9 is data showing dose dependent increase in relative caspase activity for compound 1 and ibrutinib combinations.

Figs. 10A and 10B are western blots showing a dose dependent increase in p-STAT3 levels and decrease in PIM expression for combination treatment with compound 1 and ibrutinib (10A) and no dose dependent increase in p-STAT3 levels and no significant change in PIM expression for treatment with compound 1 alone (10B).

Fig. 11 is a bar graph showing an increase in PIM expression when DOHH2 cells are treated with compound 1 and ibrutinib in combination.

DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details.

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to".

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features or characteristics may be combined in any suitable manner in one or more embodiments.

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets (e.g., cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

"Amino" refers to the $-NH_2$ radical.

"Cyano" refers to the -CN radical.

"Hydroxy" or "hydroxyl" refers to the -OH radical.

"Imino" refers to the =NH substituent.

"Nitro" refers to the $-NO_2$ radical.

"Oxo" refers to the =O substituent.

"Thioxo" refers to the =S substituent.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), having from one to twelve carbon atoms (C_1-C_{12} alkyl), preferably one to eight carbon atoms (C_1-C_8 alkyl) or one to six carbon atoms (C_1-C_6 alkyl), and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, alkyl groups are optionally substituted.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), and having from one to twelve carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, ethenylene, propenylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single or double bond and to the radical group through a single or double bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain are optionally substituted.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above containing one to twelve carbon atoms. "Haloalkoxy" is an alkoxy moiety comprising at least one halo substituent. Unless stated otherwise specifically in the specification, an alkoxy and haloalkoxy group are optionally substituted.

"Alkylamino" refers to a radical of the formula $-NHR_a$ or $-NR_aR_a$ where each R_a is, independently, an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted.

"Thioalkyl" refers to a radical of the formula $-SR_a$ where R_a is an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group may be optionally substituted.

"Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. An aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

"Aralkyl" refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group may be optionally substituted.

"Aryloxy" refers to a radical of the formula -OR_a where R_a is an aryl radical as defined above. Unless stated otherwise specifically in the specification, an aryloxy group is optionally substituted.

"Carbocyclic" refers to a ring, wherein the atoms forming the ring are each carbon. Aryl and cycloalkyl groups are carbocyclic.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

"Cycloalkylalkyl" refers to a radical of the formula -R_bR_d where R_b is an alkylene chain as defined above and R_d is a cycloalkyl radical as defined above. Unless stated otherwise specifically in the specification, a cycloalkylalkyl group may be optionally substituted.

"Fused" refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with a nitrogen atom.

"Halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

"Heterocyclyl" or "heterocyclic ring" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples

of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, Unless stated otherwise specifically in the specification, a heterocyclyl group may be optionally substituted.

"*N*-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. Unless stated otherwise specifically in the specification, a *N*-heterocyclyl group may be optionally substituted.

"Heterocyclylalkyl" refers to a radical of the formula $-R_bR_e$ where R_b is an alkylene chain as defined above and R_e is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. Unless stated otherwise specifically in the specification, a heterocyclylalkyl group may be optionally substituted.

"Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl,

pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group may be optionally substituted.

"*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an *N*-heteroaryl group may be optionally substituted.

"Heteroarylalkyl" refers to a radical of the formula $-R_bR_f$ where R_b is an alkylene chain as defined above and R_f is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkyl group may be optionally substituted.

The term "substituted" used herein means any of the above groups (*i.e.*, alkyl, alkylene, alkoxy, haloalkoxy, aryloxy, alkylamino, thioalkyl, aryl, aralkyl, carbocyclic, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-

heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents.

"Compounds of the invention" or "disclosed compounds" refers to compounds targeting PIM kinase or BTK, for example a compound of structure (I) or (II), or a compound targeting PIM kinase or BTK known in the art or incorporated by reference.

Embodiments of the present invention also includes administration of prodrugs of the disclosed compounds. "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted *in vivo* to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam)). A discussion of prodrugs is provided in Higuchi, T., et al., A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, Ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound of the invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound of the invention. Prodrugs include compounds of the invention wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention 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, acetate, formate and benzoate derivatives of alcohol or amide derivatives of amine functional groups in the compounds of the invention and the like.

Embodiments of the invention disclosed herein are also meant to encompass administration of all pharmaceutically acceptable compounds of the disclosed compounds being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of structure (I) or (II), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of structure (I) or (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Embodiments of the invention disclosed herein are also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, embodiments include compounds produced by a process comprising administering a compound of this invention to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabelled compound of the invention in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid,

sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

Often crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compound of the invention may be true solvates, while in other cases, the compound of the invention may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

"Effective amount" or "therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a mammal, preferably a human, is sufficient to effect treatment, as defined below, of a cancer, such

as a b-cell malignancy) in the mammal, preferably a human. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, the manner of administration, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes:

(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, *i.e.*, arresting its development;

(iii) relieving the disease or condition, *i.e.*, causing regression of the disease or condition; or

(iv) relieving the symptoms resulting from the disease or condition, *i.e.*, relieving pain without addressing the underlying disease or condition. As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

The compounds of the invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. Embodiments of the present invention are meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

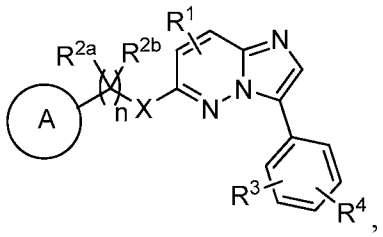
A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. Embodiments contemplate various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. Embodiments this include tautomers of any said compounds.

I. Methods

Accordingly, in one embodiment a method for treating cancer in a mammal in need thereof is provided, the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor. The structure of the PIM kinase inhibitor and BTK inhibitor is not particularly limited provided the inhibitor has satisfactory activity against the desired target (i.e., PIM or BTK). Exemplary PIM inhibitors which are included within the scope of embodiments of the present invention include the generic and specific compounds disclosed in U.S. Patent No. 7,750,007 and U.S. Pub. No. 2014/0329807, the full disclosures of which are hereby incorporated by reference in their entireties. Other PIM kinase inhibitors are known in the art, and such inhibitors are also included in certain embodiments of the invention.

In some specific embodiments, the PIM kinase inhibitor has the following structure (I):



(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

A is an optionally substituted 3-8 membered carbocyclic or heterocyclic ring;

X is $-N(R^5)-$ or -O-;

R^1 is H, -OH, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-N(R^5)_2$, or -CN;

R^{2a}, R^{2b} and R^5 are, at each occurrence, independently H or alkyl;

R^3 is halo, haloalkyl or haloalkoxy;

R^4 is H, -OH, alkyl or alkoxy; and

n is 0, 1, 2, 3 or 4.

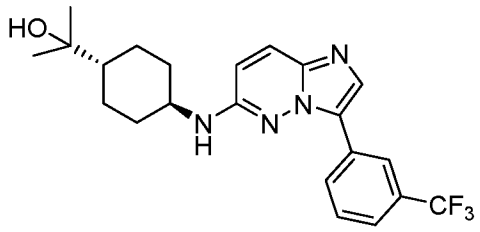
In some embodiments of compound (I), A is cyclohexyl or piperazinyl. In further embodiments, cylohexyl is substituted with hydroxylalkyl. In other embodiments, piperazinyl is substituted with methyl, such as N-methylpiperazinyl.

In various embodiments, X is NH.

In more embodiments, R^4 is H.

In some other embodiments, R^3 is trifluoromethyl. In different embodiments, R^3 is trifluoromethoxy.

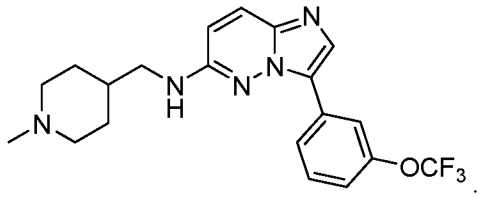
In some more specific embodiments, the PIM kinase inhibitor the following structure (1) (*i.e.*, "compound 1"):



1

or a stereoisomer or pharmaceutically acceptable salt thereof.

In some other more specific embodiments, the PIM kinase inhibitor the following structure (2) (*i.e.*, "compound 2"):



2

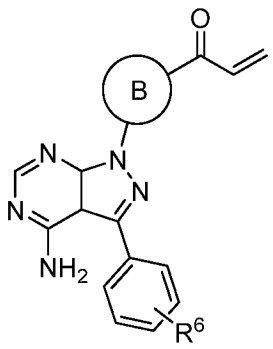
or a stereoisomer or pharmaceutically acceptable salt thereof.

The structure of the BTK inhibitor for use in the present methods is also not particularly limited provided it has sufficient activity against BTK when used in combination with the PIM inhibitor. Exemplary BTK inhibitors, all of which are included within the scope of certain embodiments of the invention, are described in PCT Pub. Nos: WO 2014/052365; WO 2015/048689; WO 2015/002894; WO 2014/168975; WO 2014/159745; WO 2014/130693; WO 2014/078578; WO 2014/018567; WO 2013/184572; WO 2013/173518; WO 2013/116382; WO 2013/102059; WO 2013/059738; WO 2013/010136; WO 2011/153514; WO 2011/046964; WO 2010/009342; WO 2008/121742; WO 2008/054827; WO

2008/039218; WO 2007/087068; and in U.S. Pub. Nos: 2015/0018336; 2014/0336206; 2014/0243355; 2014/0212485; 2014/0194446/ 2014/0187564; 2014/0135347; 2014/0128414; 2014/0187565; 2014/0171453; 2014/0163027; 2014/01663046; 2014/0142126; 2014/0142123; 2014/0128413; 2014/0079690; 2014/0080844; 2014/0057907; 2014/0039168; 2013/0338172; 2013/0310402; 2013/0273030; 2013/0197014; 2013/0035334; 2013/0012525; 2012/0283277; 2012/0283276; 2012/0277254; 2012/0252821; 2010/0331350, the full disclosures of which are hereby incorporated by reference in their entireties.

In some other embodiments, the BTK inhibitor is ONO-4059, AVL-292, SNS-062, CNX-774, CGI-1746, RN486 or ACP-196, which compounds are known in the art.

In still other embodiments, the BTK inhibitor has the following structure (II):



II

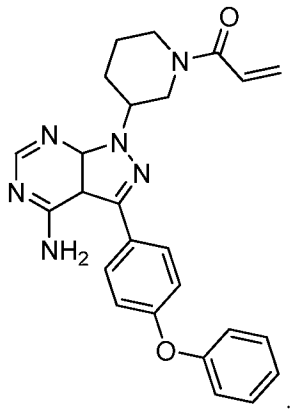
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

B is a 3-8 membered optionally substituted heterocyclic ring; and

R^6 is aryloxy.

In some embodiments of compound (II), R^6 is phenyloxy. In other embodiments, B is piperidinyl.

In some more specific embodiments, the BTK inhibitor has the following structure (3) ("ibrutinib"):



3

or a stereoisomer or pharmaceutically acceptable salt thereof.

Various different cancers can be treated by the methods disclosed herein. In some embodiments the cancer is a B-cell malignancy. In some embodiments, the cancer is a B-cell lymphoma. In other embodiments, the cancer is chronic lymphocytic leukemia (CLL).

In some different embodiments, the invention is directed to a method for decreasing the expression of c-Myc in a mammalian cell, the method comprising contacting the cell with a PIM kinase inhibitor and a BTK inhibitor. In such embodiments, the PIM kinase inhibitor the BTK inhibitor are defined according to any of the foregoing embodiments.

A wide variety of cancers, including solid tumors and leukemias (e.g., acute myeloid leukemia) are amenable to the methods disclosed herein. Types of cancer that may be treated in various embodiments include, but are not limited to: adenocarcinoma of the breast, prostate, and colon; all forms of bronchogenic carcinoma of the lung; myeloid; melanoma; hepatoma; neuroblastoma; papilloma; apudoma; choristoma; branchioma; malignant carcinoid syndrome; carcinoid heart disease; and carcinoma (e.g., Walker, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumor, Krebs 2, merkel cell, mucinous, non-small cell lung, oat cell, papillary, scirrhous, bronchiolar, bronchogenic, squamous cell, and transitional cell). Additional types of cancers that may be treated include: histiocytic disorders; leukemia; histiocytosis malignant; Hodgkin's disease; immunoproliferative small; non-Hodgkin's lymphoma; plasmacytoma; reticuloendotheliosis; melanoma; chondroblastoma; chondroma; chondrosarcoma; fibroma; fibrosarcoma; giant cell tumors; histiocytoma; lipoma; liposarcoma; mesothelioma; myxoma; myxosarcoma; osteoma; osteosarcoma; chordoma; craniopharyngioma; dysgerminoma; hamartoma; mesenchymoma; mesonephroma; myosarcoma; ameloblastoma; cementoma; odontoma; teratoma; thymoma; trophoblastic tumor. Further, the following types of cancers are also

contemplated as amenable to treatment: adenoma; cholangioma; cholesteatoma; cyclindroma; cystadenocarcinoma; cystadenoma; granulosa cell tumor; gynandroblastoma; hepatoma; hidradenoma; islet cell tumor; Leydig cell tumor; papilloma; sertoli cell tumor; theca cell tumor; leimyoma; leiomyosarcoma; myoblastoma; myomma; myosarcoma; rhabdomyoma; rhabdomyosarcoma; ependymoma; ganglioneuroma; glioma; medulloblastoma; meningioma; neurilemmoma; neuroblastoma; neuroepithelioma; neurofibroma; neuroma; paraganglioma; paraganglioma nonchromaffin. The types of cancers that may be treated also include, but are not limited to, angiokeratoma; angiolymphoid hyperplasia with eosinophilia; angioma sclerosing; angiomatosis; glomangioma; hemangioendothelioma; hemangioma; hemangiopericytoma; hemangiosarcoma; lymphangioma; lymphangiomyoma; lymphangiosarcoma; pinealoma; carcinosarcoma; chondrosarcoma; cystosarcoma phyllodes; fibrosarcoma; hemangiosarcoma; leiomyosarcoma; leukosarcoma; liposarcoma; lymphangiosarcoma; myosarcoma; myxosarcoma; ovarian carcinoma; rhabdomyosarcoma; sarcoma; neoplasms; nerofibromatosis; and cervical dysplasia.

II. Pharmaceutical compositions

Other embodiments are directed to pharmaceutical compositions. The pharmaceutical composition comprises a pharmaceutically acceptable carrier or excipient, a PIM kinase inhibitor and a BTK inhibitor. The pharmaceutical composition includes a PIM kinase inhibitor and BTK inhibitor according to any of the foregoing described embodiments.

Different embodiments also provide a kit comprising a PIM kinase inhibitor, a BTK inhibitor and instructions for administering the PIM kinase inhibitor and BTK inhibitor to a mammal in need thereof. The disclosed kits include a PIM kinase inhibitor and BTK inhibitor according to any of the foregoing described embodiments.

In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection.

Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages 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 are used in some embodiments. An exemplary dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

In some embodiments, a compound of the invention is administered in a single dose. Typically, such administration will be by injection, e.g., intravenous injection, in order to introduce the agent quickly. However, other routes are used as appropriate. A single dose of a compound of the invention may also be used for treatment of an acute condition.

In some embodiments, a compound of the invention is administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment a compound of the invention and another agent are administered together about once per day to about 6 times per day. In another embodiment the administration of a compound of the invention and an agent 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.

Administration of the compounds of the invention may continue as long as necessary. In some embodiments, a compound of the invention is administered for

more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, a compound of the invention is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, a compound of the invention is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

In some embodiments, the compounds of the invention are administered in dosages. Due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is provided in certain embodiments. Dosing for a compound of the invention may be found by routine experimentation in light of the instant disclosure and/or can be derived by one of ordinary skill in the art.

In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

Provided herein are pharmaceutical compositions comprising inhibitors (also referred to herein as compounds) targeting PIM kinase and/or BTK. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this disclosure.

A pharmaceutical composition, as used herein, refers to a mixture of an inhibitor targeting PIM kinase and/or BTK with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In some embodiments, the pharmaceutical composition comprises both a PIM kinase inhibitor and a BTK inhibitor. In other embodiments, the pharmaceutical composition comprises a PIM kinase inhibitor or a BTK inhibitor. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, therapeutically effective amounts of inhibitors targeting PIM kinase and BTK are administered in a pharmaceutical composition, together or

separately, to a mammal having a disease, disorder or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors.

In one embodiment, the compounds are formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, inhibitors targeting at least two super-enhancer components are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

In another embodiment, compounds described herein are formulated for oral administration. Compounds described herein are formulated by combining the active compounds with, e.g., pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc,

polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

In certain embodiments, therapeutically effective amounts of compounds targeting PIM kinase and BTK are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

In other embodiments, therapeutically effective amounts of compounds targeting PIM kinase and BTK are formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, the compounds disclosed herein are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (e.g., in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, suspensions of the active compounds (e.g., compounds of structure (I) or (II)) are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension

contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

In still other embodiments, the compounds targeting PIM kinase and BTK are administered topically. The compounds disclosed herein are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compositions optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

In yet other embodiments, the compounds targeting PIM kinase and BTK are formulated for transdermal administration. In specific embodiments, transdermal formulations employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In various embodiments, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In additional embodiments, the transdermal delivery of inhibitors targeting at least two super-enhancer components is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of inhibitors targeting at least two super-enhancer components. In specific embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. In alternative embodiments, absorption enhancers are used to increase absorption. Absorption enhancers or carriers include absorbable pharmaceutically acceptable solvents that assist passage through the skin. For example, in one embodiment, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

In other embodiments, compounds targeting PIM kinase and BTK are formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists or powders. Pharmaceutical compositions of inhibitors targeting at least two super-enhancer components are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In specific embodiments, the dosage unit of a

pressurized aerosol is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator are formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

In still other embodiments, compounds targeting PIM kinase and BTK are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are optionally used as suitable. Pharmaceutical compositions comprising inhibitors targeting at least two super-enhancer components are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and inhibitors targeting at least two super-enhancer components, described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds disclosed herein are included within the scope of the compounds presented herein. Additionally, the compounds disclosed herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of inhibitors targeting at least two super-enhancer components presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

Methods for the preparation of compositions comprising compounds targeting PIM kinase and BTK described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

In some embodiments, a pharmaceutical composition comprising a PIM kinase and/or BTK targeting compound illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

In certain embodiments, useful aqueous suspensions contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, e.g., hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of inhibitors targeting at least two super-enhancer components. The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400, and glycol ethers.

Furthermore, useful pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric,

citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Other useful pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

Still other useful compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

Still other useful compositions include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days.

Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is less than 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.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is 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%, 125% , 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.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is 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%, approximately 1% to approximately 10% w/w, w/v or v/v.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is 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.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is 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.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is 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, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

The PIM kinase inhibitor and BTK inhibitor can be administered concurrently or separately. For example, one of the inhibitors may be administered via a bolus followed by a separate bolus of the second inhibitor after an appropriate period of time. Slower administration, such as a longer duration infusion can be used for administration of one or both of the inhibitors. The skilled clinician can determine appropriate administration methods and orders, which are all within the scope of the present invention.

The PIM kinase inhibitors and BTK inhibitors can be prepared according to methods known in the art. Exemplary preparation procedures are provided in PCT Pub. Nos: WO 2014/052365; WO 2015/048689; WO 2015/002894; WO 2014/168975; WO 2014/159745; WO 2014/130693; WO 2014/078578; WO 2014/018567; WO 2013/184572; WO 2013/173518; WO 2013/116382; WO 2013/102059; WO 2013/059738; WO 2013/010136; WO 2011/153514; WO 2011/046964; WO 2010/009342; WO 2008/121742; WO 2008/054827; WO 2008/039218; WO 2007/087068; and in U.S. Pub. Nos: 2015/0018336; 2014/0336206; 2014/0329807; 2014/0243355; 2014/0212485; 2014/0194446/ 2014/0187564; 2014/0135347; 2014/0128414; 2014/0187565; 2014/0171453; 2014/0163027; 2014/01663046; 2014/0142126; 2014/0142123; 2014/0128413; 2014/0079690; 2014/0080844; 2014/0057907; 2014/0039168; 2013/0338172; 2013/0310402; 2013/0273030; 2013/0197014; 2013/0035334; 2013/0012525; 2012/0283277; 2012/0283276; 2012/0277254; 2012/0252821; 2010/0331350, and U.S. Patent No. 7,750,007, the full disclosures of which are hereby incorporated by reference in their entireties.

EXAMPLES

EXAMPLE 1

COMPOUND 1 SHOWS ACTIVITY AGAINST MULTIPLE CELL TYPES AND LINES

Compound 1 was tested for its individual IC50 inhibitory activity against multiple cell types and lines using methods known in the art, for example as described in U.S. Pub. No 2014/0329807, which is incorporated by reference in its entirety. Compound 1 was tested in 10-dose IC50 mode with 3-fold serial dilution starting at 20 μm. The results presented in Figure 2 demonstrate that compound 1 has activity against a wide variety of cell lines and types when administered as a single agent.

EXAMPLE 2

COMPOUND 1 IS ACTIVE AGAINST ALL THREE PIM ISOFORMS AND PI3K

Compound 1 was tested for inhibitory activity against different PIM isoforms and PI3K according to the general procedures described in Example 1. Figures 3A and 3B provide the IC50 curves for compound 1 against PIM1 and PIM3, respectively. Figure 4 provides the IC50 curve for activity of compound 1 against PI3K (α, β, γ and δ). Activity of compound 1 against PI3K was evidenced by a decrease in in p-AKT levels in PC3 cells (Fig. 5). Table 1 below provides IC50 data for compound 1 against PIM and PI3K.

Table 1. IC50 Data for Compound 1

Kinases	Compound IC50 (nM)
PIM-1	11
PIM-2	564
PIM-3	13
PI3Kalpha	191
PI3Kbeta	790

Kinases	Compound IC50 (nM)
PI3Kgamma	60
PI3Kdelta	87

EXAMPLE 3

COMPOUND 1 DECREASES C-MYC EXPRESSION

The effectiveness of compound 1 to inhibit c-Myc expression as a single agent was determined as follows. Granta-4 cells were treated with compound 1 for 24 hours, followed by stimulation with IL-22 at 20 μg/mL. Figs. 6A and 6B present western blot (6A) and quantitative analysis of a western blot (6B), respectively, for c-Myc expression by compound 1.

EXAMPLE 4

SINGLE AGENT ACTIVITY OF COMPOUND 1 AND IBRUTINIB AGAINST MULTIPLE B-CELL MALIGNANCIES

The effectiveness of compound 1 and ibrutinib as single agents against multiple B-cell malignancies was determined by treating cells with varying concentrations (30 μM to 0.001μM) of compound 1 or ibrutinib for 24 hours. Fig. 7A provides cell viability data for DOHH2 (0.3 μM), Granta 4 (12.4 μM) and Granta 519 (11.1 μM) cells when treated with compound 1 alone, while Fig. 7B provides analogous data for DOHH2 (2.9 μM), Granta 4 (5.0 μM) and Granta 519 (7.7 μM) cells treated with ibrutinib alone.

EXAMPLE 5

COMPOUND 1 AND IBRUTINIB ARE SYNERGISTIC AGAINST GRANTA-519 CELLS

Synergism between compound 1 and ibrutinib was tested as follows. Shifting IC50 curves suggests synergism between PIM and BTK inhibition. Granta-519 cells were treated for 72 hours with sub-toxic doses of ibrutinib, and varying concentrations of compound 1, between 30 μM and 0.001 μM. IC50 curves shift from 1.2 to 0.4 μM, between the two curves (Fig. 8A). Granta-519 cells were treated for 72 hours with sub-toxic doses of compound 1, and varying concentrations of ibrutinib between 30 μM and 0.001 μM. IC50 curves shift from 1.0 to 0.2 μM, between the two curves (Fig. 8B).

Shifting IC50 curves in Figs. 8A and 8B suggests unexpected synergism between PIM and BTK inhibition.

EXAMPLE 6

COMPOUND 1 AND IBRUTINIB COMBINATIONS SHOW A DOSE DEPENDENT INCREASE IN RELATIVE CAPASE ACTIVITY

DOHH2 cells were cultured for 24 hours with compound 1 and ibrutinib in combination. Compound 1 concentration was varied between 30 μM and no treatment. The data provided in Figure 9 supports a dose dependent increase in relative caspase activity of compound 1 and ibrutinib in combination.

EXAMPLE 7

MODULATION OF P-STAT3 AND PIM-1 LEVELS WITH COMBINATIONS OF COMPOUND 1 AND IBRUTINIB

Granta-519 cells were treated for 24 hours at 0.3 μM ibrutinib, and varying concentrations of Compound 1. Western blot data confirmed a dose dependent increase in p-STAT3 levels, with a concomitant decrease in levels of PIM expression when compound 1 and ibrutinib are used in combination (Fig 10A). Analogous experiments performed without ibrutinib (i.e., compound 1 as a single agent) showed no dose dependent increase in p-STAT3 levels, and no significant change in levels of PIM expression (Fig. 10B).

PIM-1 EXPRESSION IS MODULATED BY COMBINATIONS OF COMPOUND 1 AND IBRUTINIB

DOHH2 cells were cultured for 24 hours with compound 1 and ibrutinib at varying concentrations. The data in Figure 11 confirms PIM-1 modulation by the combination of compound 1 and ibrutinib.

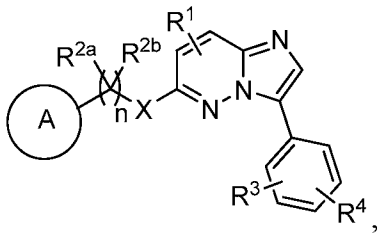
All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety to the extent not inconsistent with the present description.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. A method for treating cancer in a mammal in need thereof, the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor.

2. The method of claim 1, wherein the PIM kinase inhibitor has the following structure (I):



(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

A is an optionally substituted 3-8 membered carbocyclic or heterocyclic ring;

X is $-N(R^5)-$ or -O-;

R^1 is H, -OH, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, $-N(R^5)_2$, or -CN;

R^{2a}, R^{2b} and R^5 are, at each occurrence, independently H or alkyl;

R^3 is halo, haloalkyl or haloalkoxy;

R^4 is H, -OH, alkyl or alkoxy; and

n is 0, 1, 2, 3 or 4.

3. The method of claim 2, wherein A is cyclohexyl or piperazinyl.

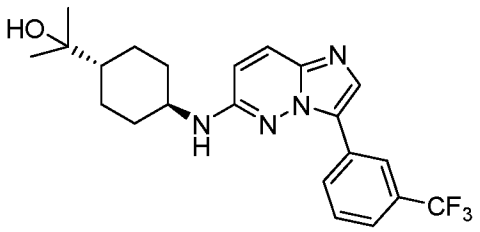
4. The method of claim 3, wherein cylohexyl is substituted with hydroxylalkyl, and piperazinyl is substituted with methyl.

5. The method of any one of claims 2-4, wherein X is NH.

6. The method of any one of claims 2-5, wherein R^4 is H.

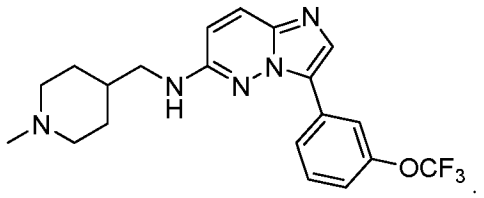
7. The method of any one of claims 2-6, wherein R^3 is trifluoromethyl or trifluoromethoxy.

8. The method of any one of claims 1-7, wherein the PIM kinase inhibitor has one of the following structures (1) or (2):



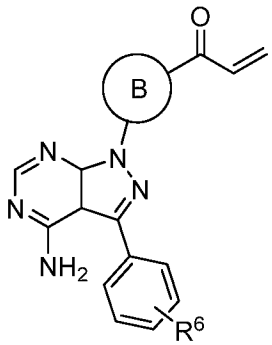
1

or



2

9. The method of any one of claims 1-8, wherein the BTK inhibitor has the following structure (II):



II

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

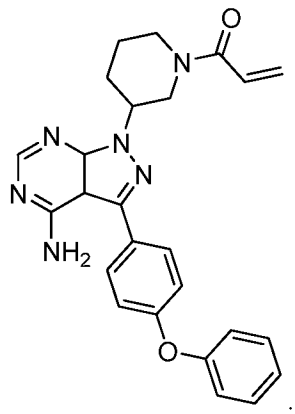
B is a 3-8 membered optionally substituted heterocyclic ring; and

R^6 is aryloxy.

10. The method of claim 9, wherein R^6 is phenyloxy.

11. The method of any one of claims 9 or 10, wherein B is piperidinyl.

12. The method of any one of claims 1-11, wherein the BTK inhibitor has the following structure (3):



3

13. The method of any one of claims 1-12, wherein the cancer is a B-cell malignancy.

14. The method of claim 13, wherein the cancer is a B-cell lymphoma.

15. The method of claim 14, wherein the cancer is chronic lymphocytic leukemia (CLL).

16. A method for decreasing the expression of c-Myc in a mammalian cell, the method comprising contacting the cell with a PIM kinase inhibitor and a BTK inhibitor.

17. The method of claim 16, wherein the PIM kinase inhibitor is as defined in any one of claims 2-8, and the BTK inhibitor is as defined in any one of claims 9-12.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient, a PIM kinase inhibitor and a BTK inhibitor.

19. The pharmaceutical composition of claim 18, wherein the PIM kinase inhibitor is as defined in any one of claims 2-8, and the BTK inhibitor is as defined in any one of claims 9-12.

20. A kit comprising a PIM kinase inhibitor, a BTK inhibitor and instructions for administering the PIM kinase inhibitor and BTK inhibitor to a mammal in need thereof.

21. The kit of claim 20, wherein the PIM kinase inhibitor is as defined in any one of claims 2-8, and the BTK inhibitor is as defined in any one of claims 9-12.

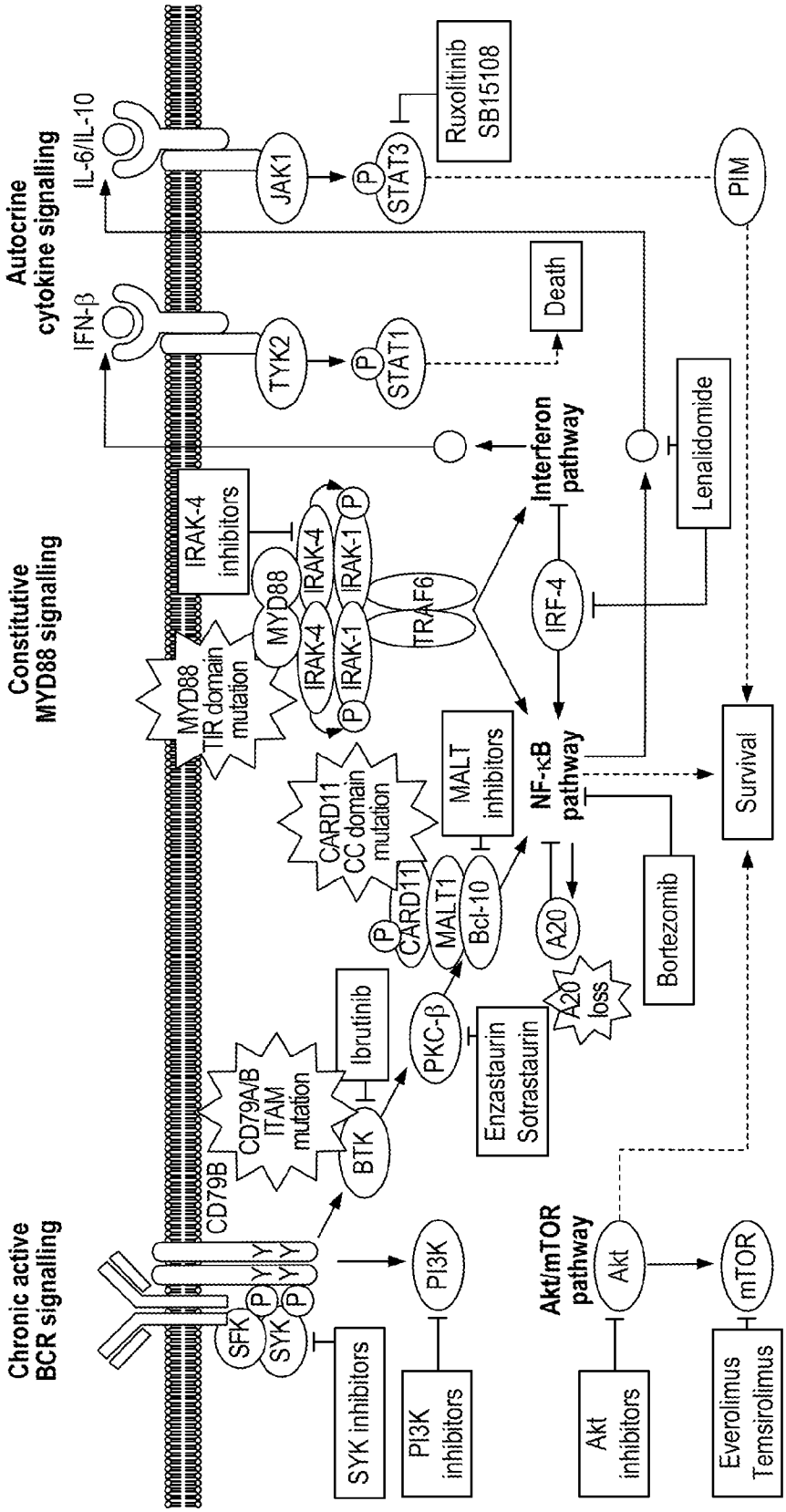

Autocrine cytokine signalling
IL-6/IL-10
IFN-β
JAK1
TYK2
STAT3
STAT1
Ruxolitinib SB15108
Death
PIM
Constitutive MYD88 signalling
MYD88 TIR domain mutation
MYD88
IRAK-4
IRAK-1
TRAF6
IRAK-4 inhibitors
Interferon pathway
IRF-4
Lenalidomide
CARD11 CC domain mutation
CARD11
MALT1
Bcl-10
MALT inhibitors
NF-κB pathway
A20
A20 loss
Bortezomib
Survival
Chronic active BCR signalling
CD79B
CD79A/B ITAM mutation
SFK
SYK
BTK
Ibrutinib
PKC-β
Enzastaurin Sotrastaurin
SYK inhibitors
PI3K
PI3K inhibitors
Akt/mTOR pathway
Akt
mTOR
Akt inhibitors
Everolimus Temsirolimus

Fig. 1

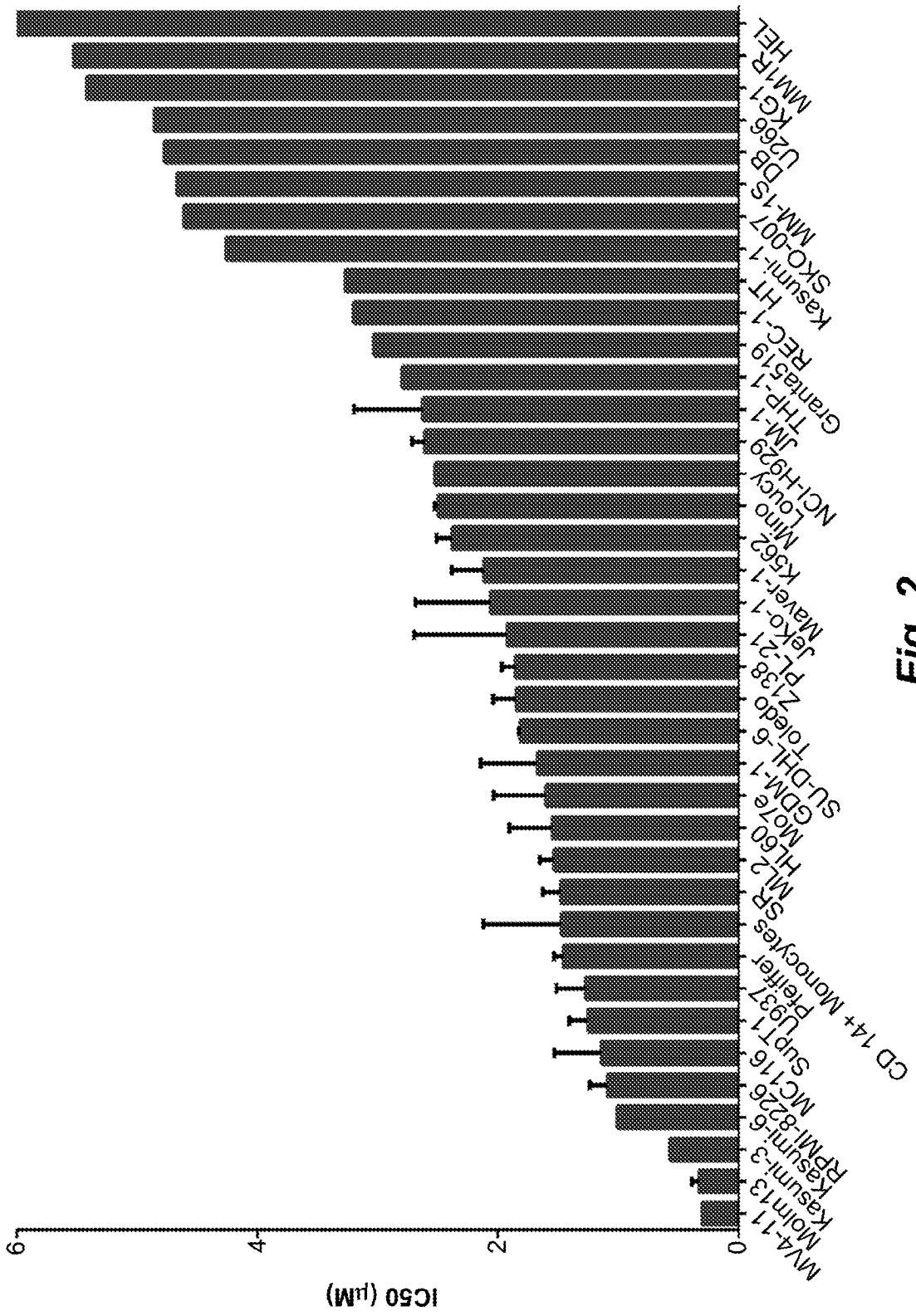

IC50 (μM)
0
2
4
6
MV4-11
Molm13
Kasumi-3
RPMI-8226
MC116
SupT1
U937
Pfeiffer
CD 14+ Monocytes
SR
ML2
HL60
MOLE
GDM-1
SU-DHL-6
Toledo
Z138
PL-21
Jeko-1
Mayer-1
K562
Mino
Loucy
NCI-H929
JM-1
THP-1
Granta519
REC-1
HT
Kasumi-1
SKO-007
MM.1S
DB
U266
KG1
MM.1R
HEL

Fig. 2

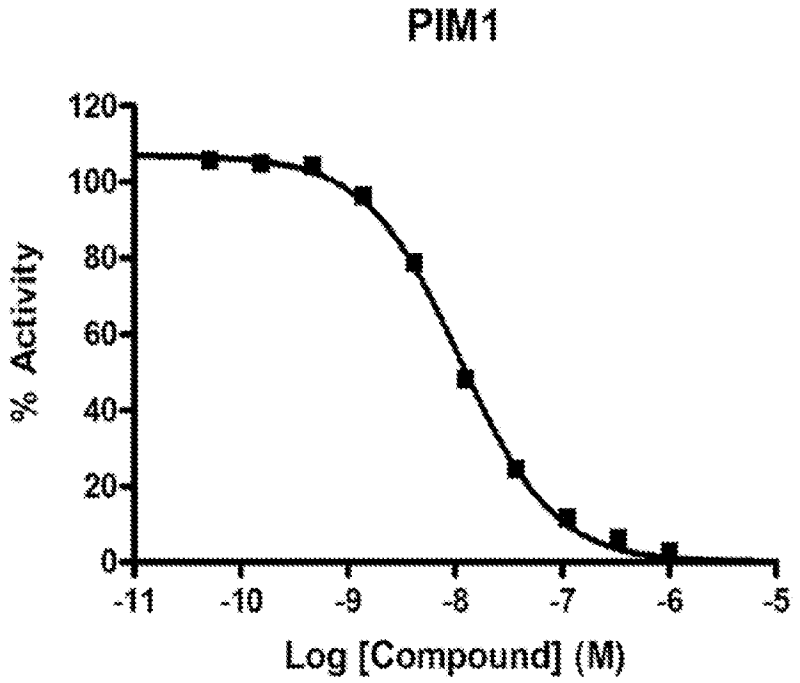

PIM1
120
100
80
60
40
20
0
% Activity
-11
-10
-9
-8
-7
-6
-5
Log [Compound] (M)

Fig. 3A

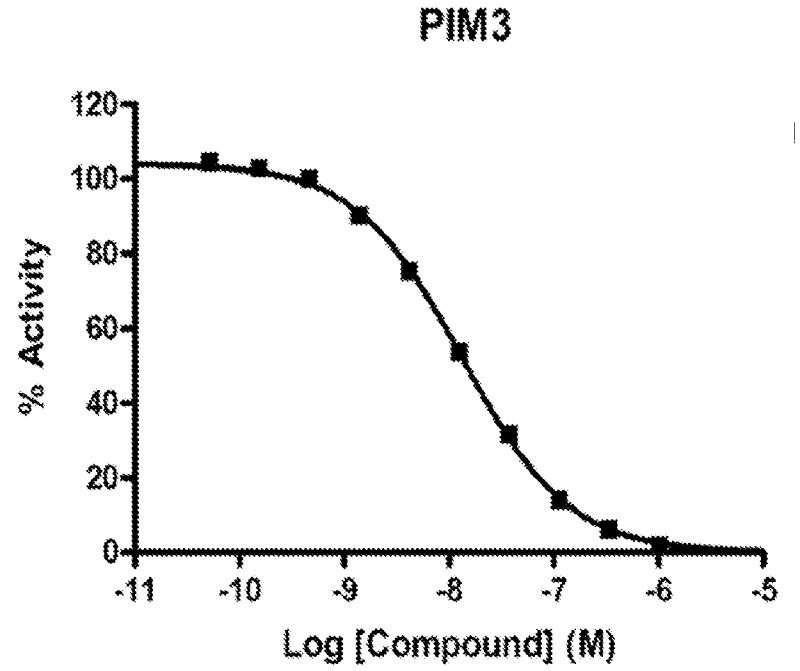

PIM3
120
100
80
60
40
20
0
% Activity
-11
-10
-9
-8
-7
-6
-5
Log [Compound] (M)

Fig. 3B

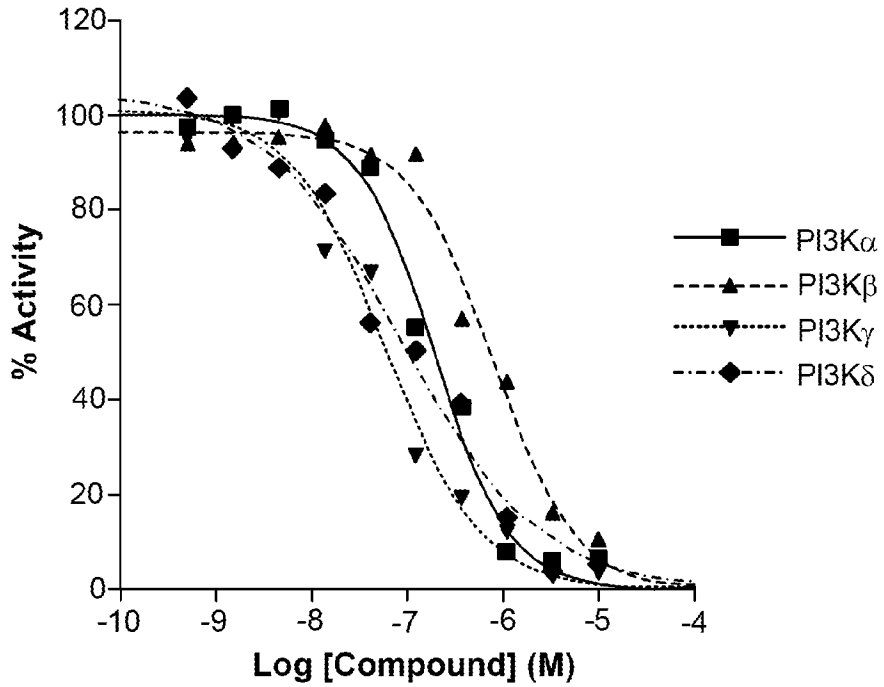

120
100
80
60
40
20
0
% Activity
-10
-9
-8
-7
-6
-5
-4
Log [Compound] (M)
PI3Kα
PI3Kβ
PI3Kγ
PI3Kδ

Fig. 4

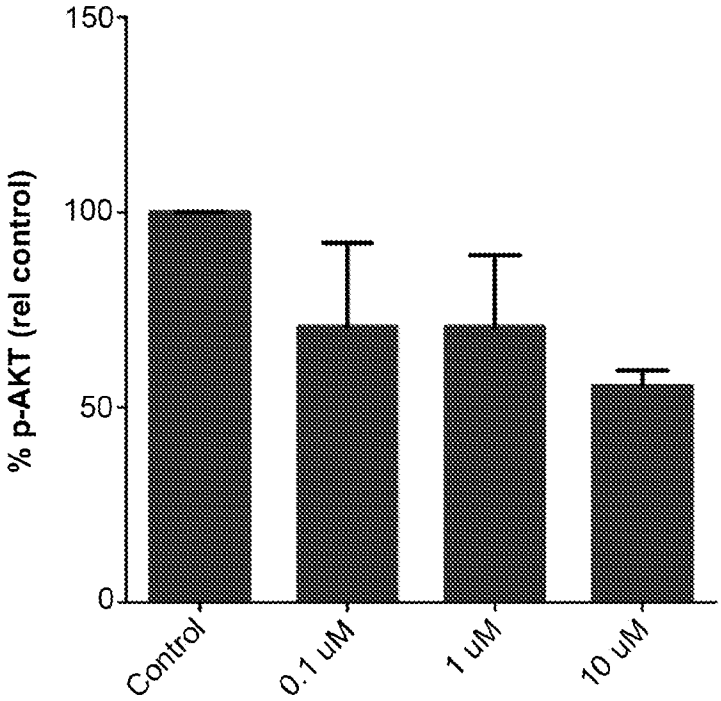

150
100
50
0
% p-AKT (rel control)
Control
0.1 uM
1 uM
10 uM

Fig. 5

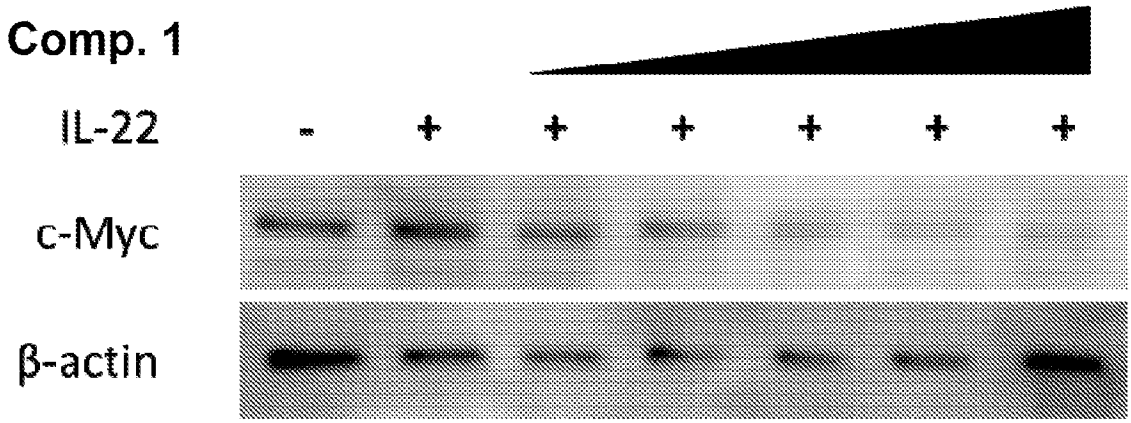

Comp. 1
IL-22
- + + + + + +
c-Myc
β-actin

Fig. 6A

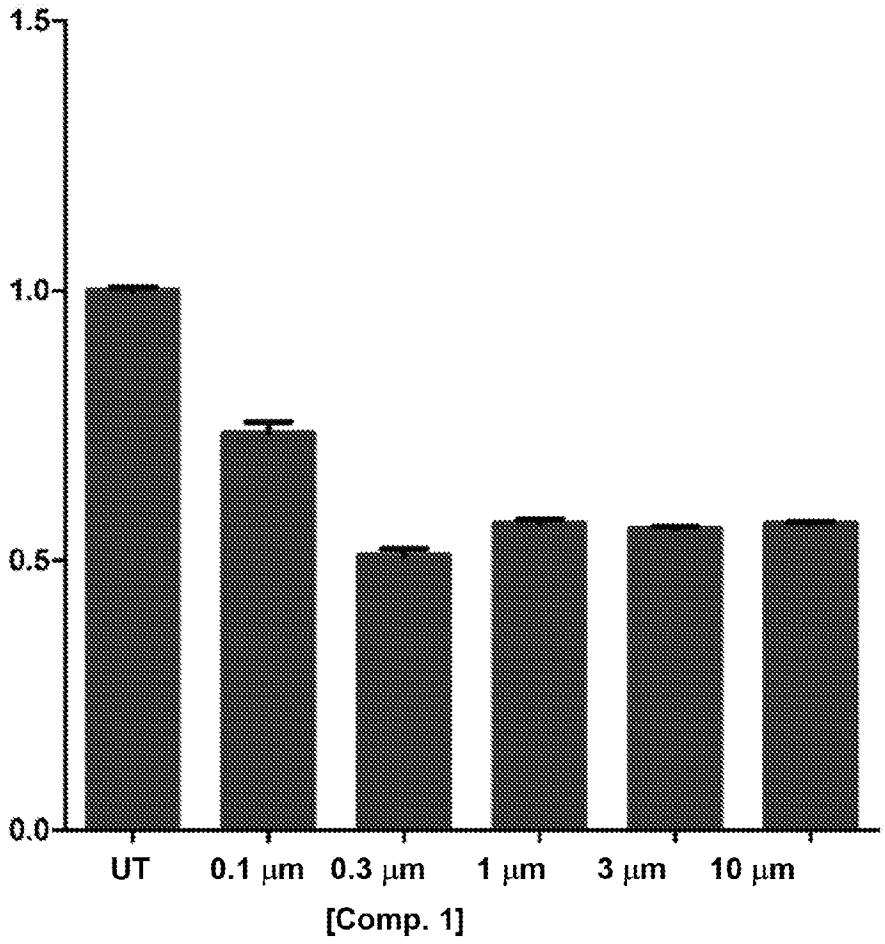

1.5
1.0
0.5
0.0
UT
0.1 μm
0.3 μm
1 μm
3 μm
10 μm
[Comp. 1]

Fig. 6B

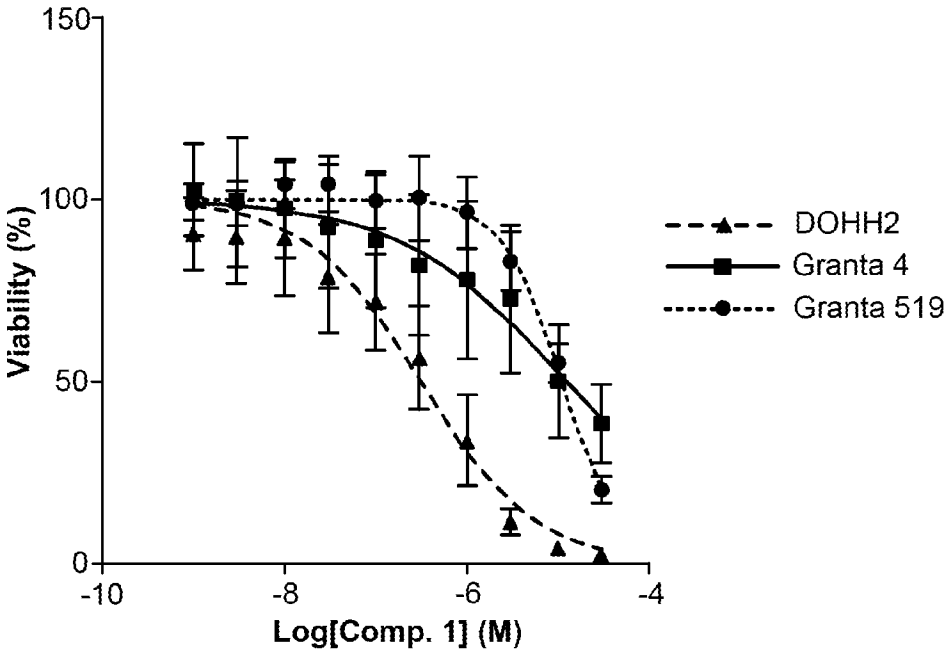

150
100
50
0
Viability (%)
-10
-8
-6
-4
Log[Comp. 1] (M)
DOHH2
Granta 4
Granta 519

Fig. 7A

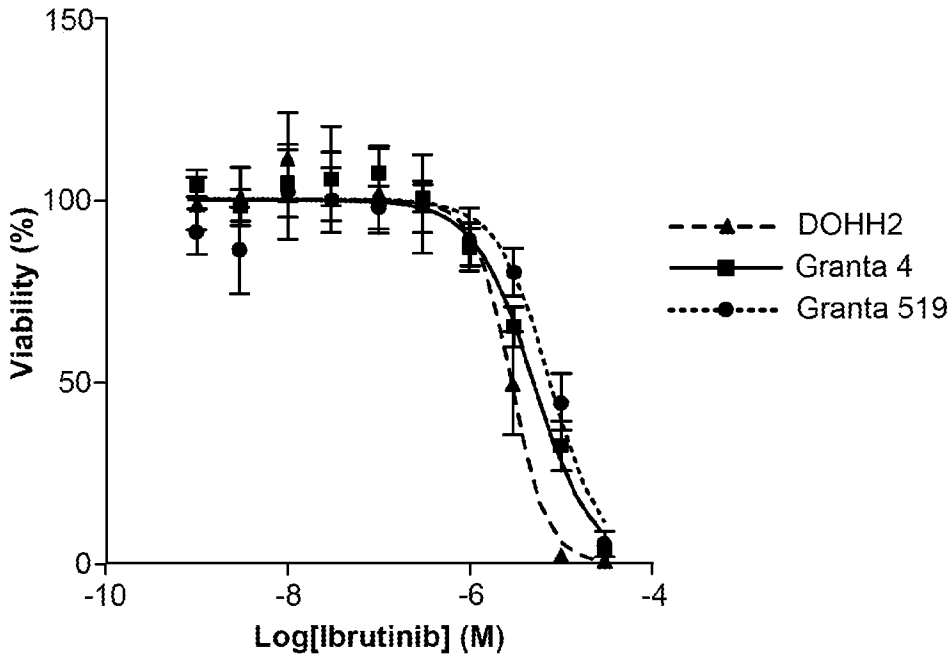

150
100
50
0
Viability (%)
-10
-8
-6
-4
Log[Ibrutinib] (M)
DOHH2
Granta 4
Granta 519

Fig. 7B

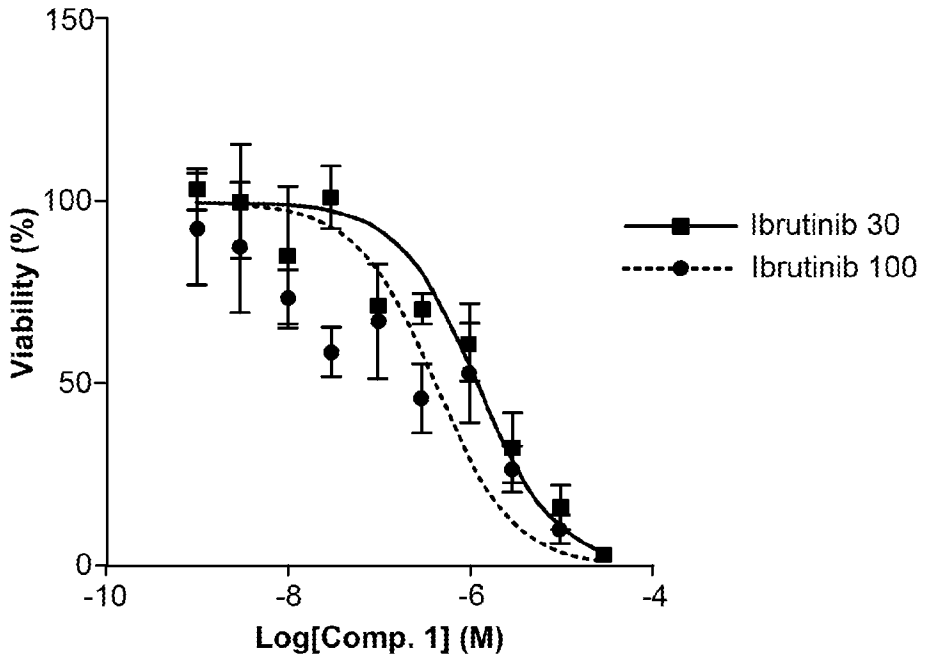

150
100
50
0
Viability (%)
-10
-8
-6
-4
Log[Comp. 1] (M)
Ibrutinib 30
Ibrutinib 100

Fig. 8A

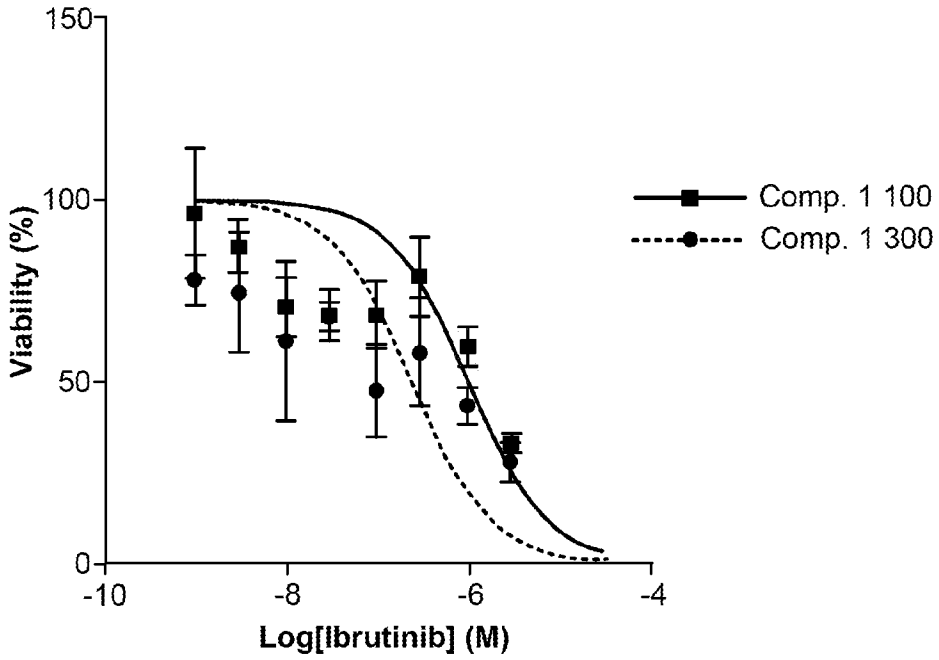

150
100
50
0
Viability (%)
-10
-8
-6
-4
Log[Ibrutinib] (M)
Comp. 1 100
Comp. 1 300

Fig. 8B

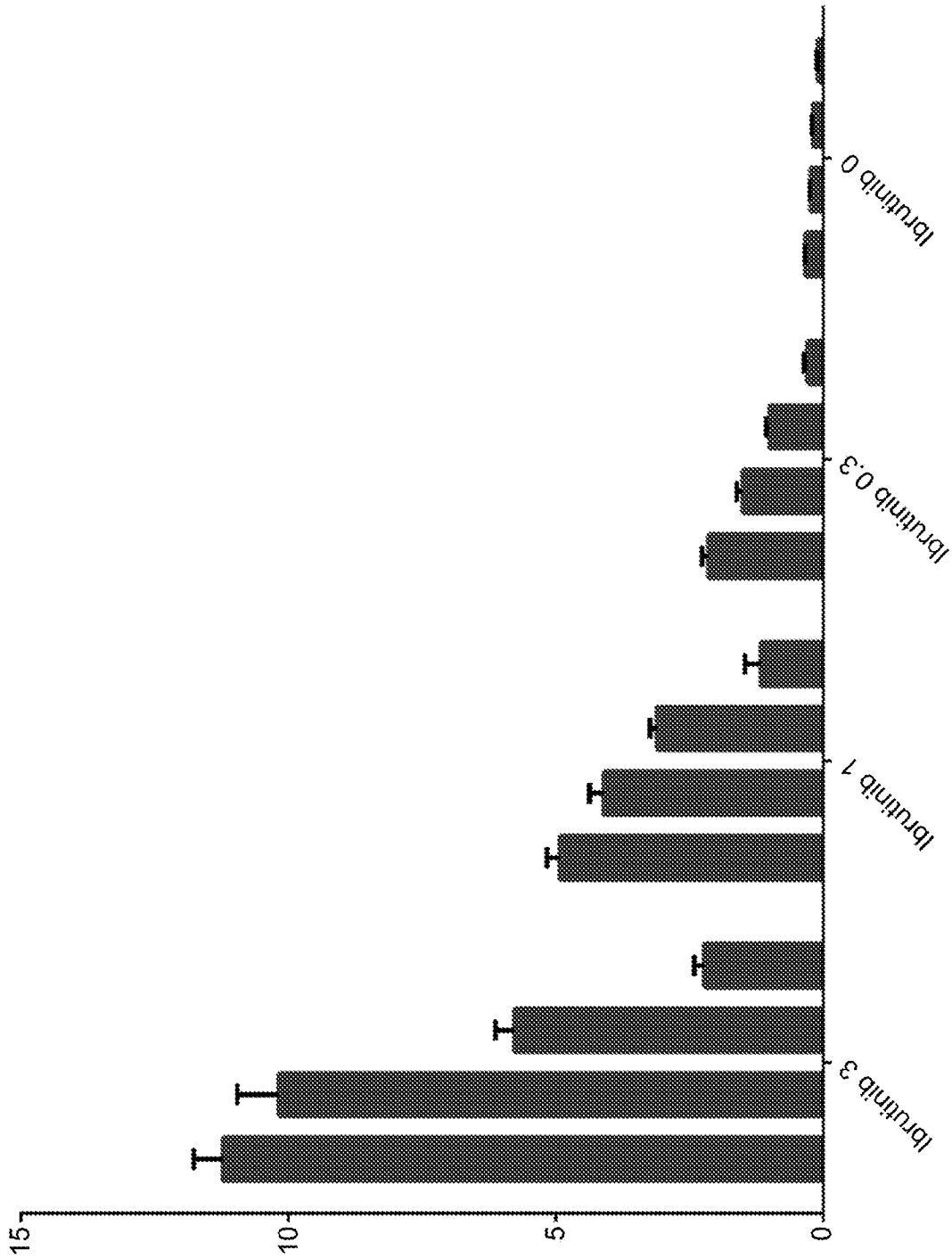


Fig. 9

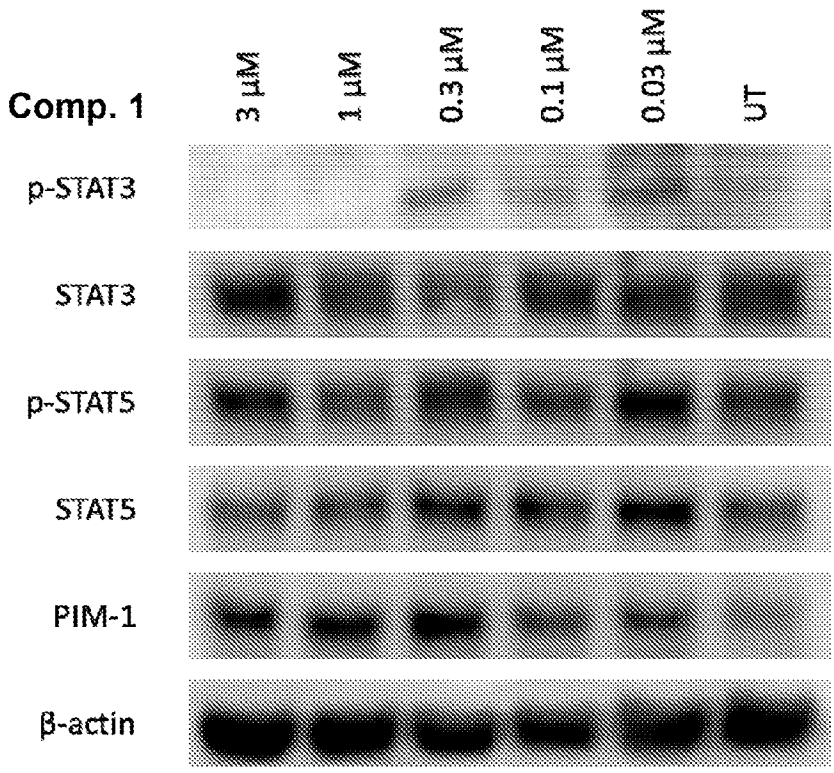


Fig. 10A

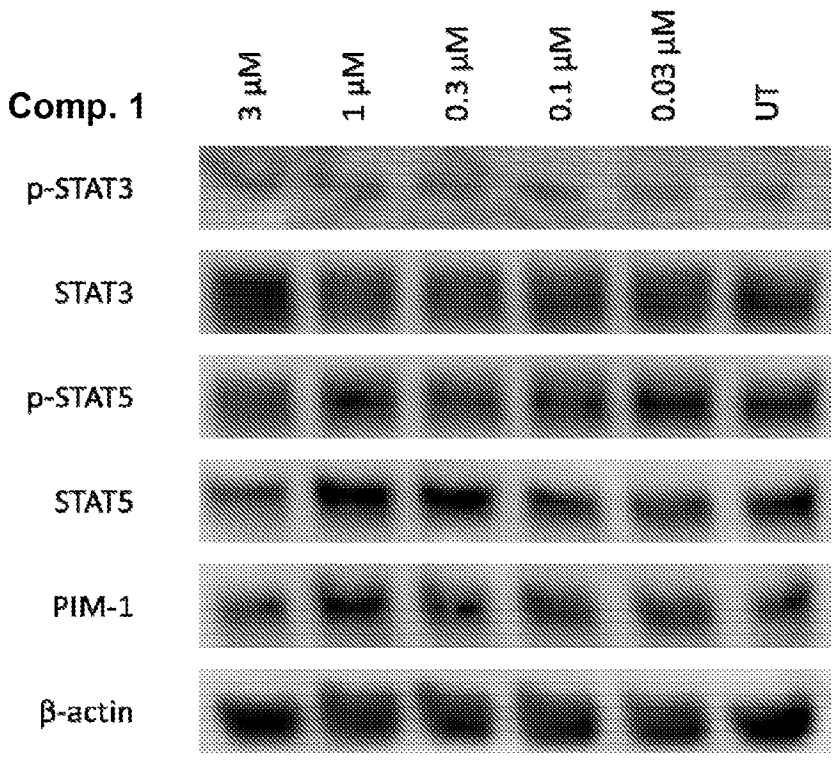


Fig. 10B

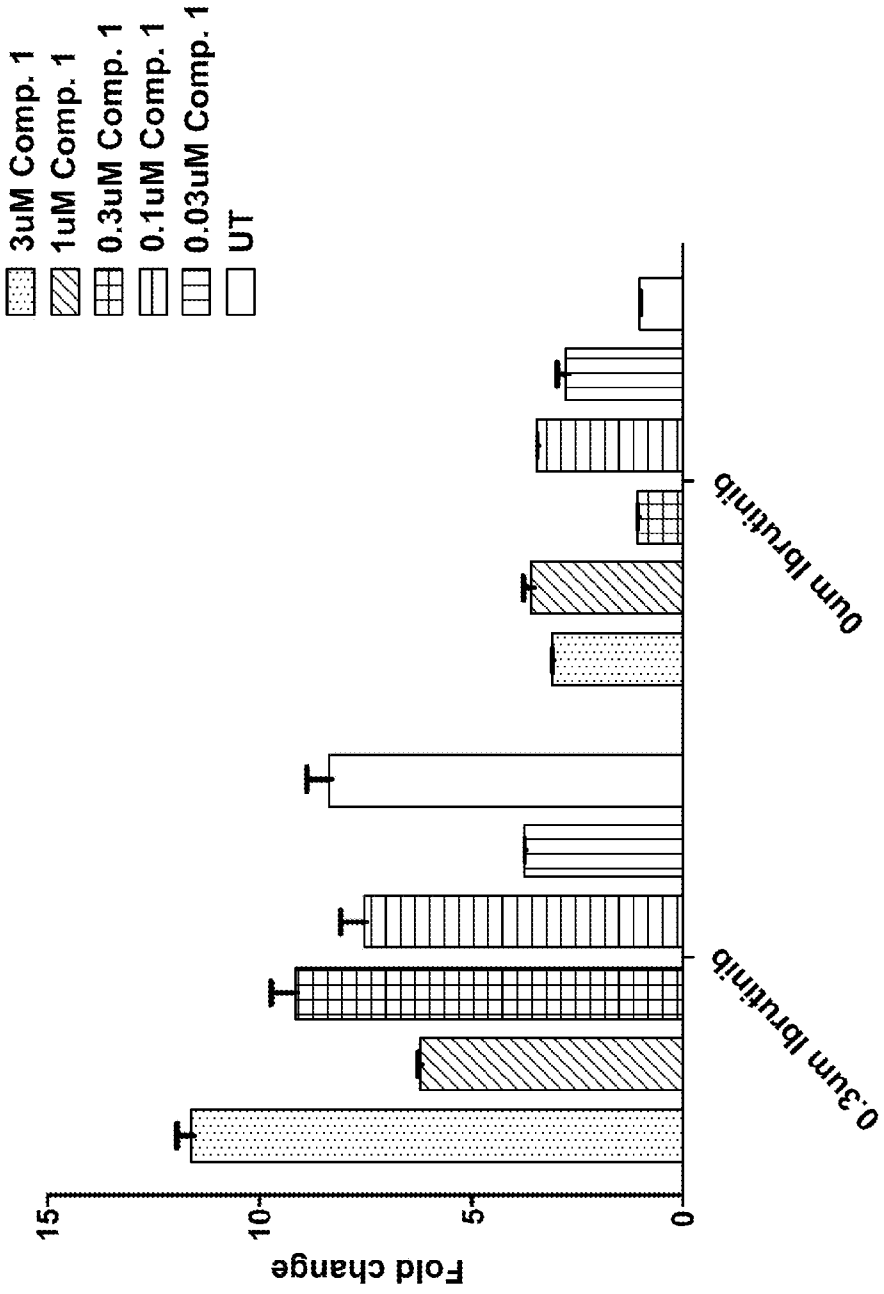

3uM Comp. 1
1uM Comp. 1
0.3uM Comp. 1
0.1uM Comp. 1
0.03uM Comp. 1
UT
Fold change
15
10
5
0
0.3um Ibrutinib
0um Ibrutinib

Fig. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/025496

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 35/00; A61K 31/4985; A61K 31/519; C07D 471/04 (2016.01)
CPC - A61K 31/4985; A61K 31/519; C07D 471/04 (2016.05)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC - A61K 31/4985; A61K 31/519; A61P 35/00; C07D 471/04
CPC - A61K 31/4985; A61K 31/519; C07D 471/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/248; 514/258.1; 514/262.1; IPC - A61K 31/4985; A61K 31/519; A61P 35/00; C07D 471/04; CPC - A61K 31/4985; A61K 31/519; C07D 471/04 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, STN, Google Scholar, PubChem
Search terms used: cancer combination therapy, PIM, Bruton, BTK, pyrazolopyrimidine, imidazopyridine, imidazo, pyrimidine, amine, ONO 4059, AVL 292, SNS-062, CNX-774, CGI-1746, ACP-196, RN-486, pyrazolo

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/0200216 A1 (INCYTE CORPORATION) 14 July 2014 (14.07.2014) entire document	1, 2, 5, 16, 18, 20
A	WO 2014/052365 A1 (MANNKIND CORPORATION) 03 April 2014 (03.04.2014) entire document	1, 2, 5, 16, 18, 20
A	US 6,921,763 B2 (HIRST et al) 26 July 2005 (26.07.2005) entire document	1, 2, 5, 16, 18, 20
A	US 7,514,444 B2 (HONIGBERG et al) 07 April 2009 (07.04.2009) entire document	1, 2, 5, 16, 18, 20
A	US 2014/0256733 A1 (CALIFIA BIO, INC) 11 September 2014 (11.09.2014) entire document	1, 2, 5, 16, 18, 20
A	BAILON et al. Src kinases catalytic activity regulates proliferation, migration and invasiveness of MDA-MB-231 breast cancer cells. Cell Signal 24(6):1276-1286, 2012 [retrieved on 10.05.2016]. Retrieved from the Internet. <URL: http://www.ncbi.nlm.nih.gov/pubmed/22570868> Abstract	1, 2, 5, 16, 18, 20
A	SHI et al. Cell-Based Proteome Profiling of Potential Dasatinib Targets by Use of Affinity-Based Probes. J. Am. Chem. Soc. 134(6): 3000-3014, 2012 [retrieved on 10.05.2016]. Retrieved from the Internet. <URL: http://pubs.acs.org/doi/abs/10.1021/ja208518u>. Abstract	1, 2, 5, 16, 18, 20

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2016	30 AUG 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/025496

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

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

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

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

3. ☒ Claims Nos.: 6-15, 17, 19, 21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

Claims 1, 2, 5, 16, 18, and 20 have been analyzed subject to the restriction that the claims read on the formulae (I) and (II) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a method for treating cancer in a mammal in need thereof, the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor, wherein the PIM kinase inhibitor has the structure (I): or a pharmaceutically acceptable salt or stereoisomer thereof, wherein: A is unsubstituted 3-membered carbocyclic ring; X is –N(R5)-; R1 is H; R2a and R2b are absent, R5 is H; R3 is halo; R4 is H; and n is 0; and wherein the BTK inhibitor has the structure (II): or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is a 3 membered unsubstituted heterocyclic ring; and R6 is aryloxy, wherein the aryloxy is phenyloxy.

See Extra Sheet

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 5, 16, 18, 20

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/025496

Continued from Box No. III Observations where unity of invention is lacking

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

Group I+: claims 1-5, 16, 18, and 20 are drawn to methods for treating cancers, pharmaceutical compositions thereof, and kits thereof.

The first invention of Group I+ is restricted to a method for treating cancer in a mammal in need thereof, the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor, wherein the PIM kinase inhibitor has the structure (I): or a pharmaceutically acceptable salt or stereoisomer thereof, wherein: A is unsubstituted 3-membered carbocyclic ring; X is –N(R5)-; R1 is H; R2a and R2b are absent, R5 is H; R3 is halo; R4 is H; and n is 0; and wherein the BTK inhibitor has the structure (II): or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is a 3 membered unsubstituted heterocyclic ring; and R6 is aryloxy, wherein the aryloxy is phenyloxy; methods thereof; pharmaceutical compositions thereof; and kits thereof. It is believed that claims 1, 2, 5, 16, 18, and 20 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would a method for treating cancer in a mammal in need thereof, the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor, wherein the PIM kinase inhibitor has the structure (I): or a pharmaceutically acceptable salt or stereoisomer thereof, wherein: A is unsubstituted 8-membered carbocyclic ring; X is -O-; R1 is -OH; R2a and R2b are at each occurrence independently alkyl; R3 is halo; R4 is -OH; and n is 4; and wherein the BTK inhibitor has the structure (II): or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is a 8 membered unsubstituted heterocyclic ring; and R6 is aryloxy, wherein the aryloxy is phenyloxy; methods thereof; pharmaceutical compositions thereof; and kits thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the PIM kinase inhibitor and BTK inhibitor.

The Groups I+ share the technical features of a method for treating cancer in a mammal in need thereof, the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor; a method for decreasing the expression of c-Myc in a mammalian cell, the method comprising contacting the cell with a PIM kinase inhibitor and a BTK inhibitor; a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient, a PIM kinase inhibitor and a BTK inhibitor; and a kit comprising a PIM kinase inhibitor, a BTK inhibitor and instructions for administering the PIM kinase inhibitor and BTK inhibitor to a mammal in need thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2014/052365 A1 to Mannkind Corporation teaches a method for treating cancer in a mammal in need thereof (Pg. 10, Lns., Paras. 2 and 3, Thus a compound inhibiting at least one of these kinases could be useful in combination with imatinib or dasatinib in treating such resistant cancers.; Claims 25, 27, and 30), the method comprising administering to the mammal an effective amount of a PIM kinase inhibitor and a BTK inhibitor (Pg. 10, Lns., Paras. 2 and 3, Thus a compound inhibiting at least one of these kinases could be useful in combination with imatinib or dasatinib in treating such resistant cancers.; Pg. 149, Therapeutic Methods and Uses; first paragraph; dasatinib inhibits PIM kinase as evidenced by "Cell-Based Proteome Profiling of Potential Dasatinib Targets by Use of Affinity-Based Probes" to Shi et al.); a method for decreasing the expression of c-Myc in a mammalian cell (Pg. 10, Lns., Paras. 2 and 3, Thus a compound inhibiting at least one of these kinases could be useful in combination with imatinib or dasatinib in treating such resistant cancers.; Claims 25, 27, and 30; Pg. 149, Therapeutic Methods and Uses; first paragraph; dasatinib decreases the expression of c-Myc as evidenced by "Src kinases catalytic activity regulates proliferation, migration and invasiveness of MDA-MB-231 breast cancer cells" to Bailon et al.), the method comprising contacting the cell with a PIM kinase inhibitor and a BTK inhibitor Pg. 10, Lns., Paras. 2 and 3, Thus a compound inhibiting at least one of these kinases could be useful in combination with imatinib or dasatinib in treating such resistant cancers.; Pg. 149, Therapeutic Methods and Uses; first paragraph); and a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient, a PIM kinase a pharmaceutical composition (Pg. 146, Para. 1) comprising a pharmaceutically acceptable carrier or excipient (Pg. 146, Para. 1), a PIM kinase inhibitor and a BTK inhibitor (Pg. 10, Lns., Paras. 2 and 3, Thus a compound inhibiting at least one of these kinases could be useful in combination with imatinib or dasatinib in treating such resistant cancers.; Pg. 149, Therapeutic Methods and Uses; first paragraph).

Additionally, US 2014/0200216 A1 to Incyte Corporation teaches a kit (Para. [0434]) comprising a PIM kinase inhibitor (Para. [0434]) and instructions for administering the PIM kinase inhibitor to a mammal in need thereof (Para. [0434]; Paras. [0401] and [0418]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.