37°C with 5% CO_2. After 72 hours of culture, cell viability was determined using an (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The potential synergy of the combination of the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX at a given equimolar concentration was determined using the median effect model as described in Chou and Talalay, *Adv Enzyme Regul.* **1984,** *22,* 27-55. The statistical modeling was run in R using a script that utilizes the median effect model as described in Lee et al., *J. Biopharm. Stat.* **2007,** *17,* 461-80. A value of 1, less than 1, and greater than 1 using R defines an additive interaction, synergistic and antagonistic, respectively. The Lee et al. method calculates a 95% confidence interval for each data point. For each viability curve, to be considered synergistic, a data point must have an interaction index below 1 and the upper confidence interval must also be below 1. In order to summarize and demonstrate collective synergy results, an interaction dot blot was generated for the primary patient samples.

[00297] A similar approach was utilized to study diffuse large B cell lymphoma (DLBCL) (TMD8) and MCL (MINO) cell lines. Cells were treated with each drug alone and with six equimolar concentrations of the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX ranging from 0.003 nM to 1.0 μM (for TMD8) or 0.03 nM to 10 μM (for MINO) on 96-well plates in triplicate. Plated cells were then cultured in standard conditioned media plus FBS at 37°C with 5% CO_2. After 72 hours of culture, viability was determined using an MTS assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The results of the experiments described in this example are shown in FIG. 1, FIG. 2, FIG. 3, and FIG. 4.

Example 2 – Synergistic Combination of a BTK inhibitor and a PI3K-δ inhibitor

[00298] Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the Chou/Talalay method/algorithm by defining combination indexes for drug combinations. Information about experimental design for evaluation of synergy is described in e.g. Chou and Talalay, *Adv. Enzyme Regul.* **1984,** *22,* 27-55 and more generally in e.g. Greco et al., *Pharmacol. Rev.* **1995,** *47,* 331-385. The study was performed using the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula

(IX). Single agent activities were first determined in the various cell lines and subsequently, the combination indexes were established using equimolar ratios taking the single agent drug EC50s into consideration. For individual agents that displayed no single agent activity, equimolar ratios were used at fixed concentrations to establish combination indexes. The readout from 72 hour proliferation assays using Cell TiterGlo (ATP content of remaining cells) determined the fraction of cells that were effected as compared to untreated cells (Fa = fraction affected = (1- ((cells + inhibitor) – background signal) / ((cells + DMSO) – background signal)).

[00299] The combination index obtained was ranked according to Table 1.

TABLE 1. Combination Index (CI) Ranking Scheme

Range of CI	Description
<0.1	Very strong synergism
0.1-0.3	Strong synergism
0.3-0.7	Synergism
0.7-0.85	Moderate synergism
0.85-0.9	Slight synergism
0.9-1.1	Nearly additive
1.1-1.2	Slight antagonism
1.2-1.45	Moderate antagonism
1.45-3.3	Antagonism
3.3-10	Strong antagonism
>10	Very strong antagonism

[00300] The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are given in FIG. 5 to FIG. 37. The results of the cell line studies are summarized in Table 2.

TABLE 2. Summary of results of the combination of a BTK inhibitor with a PI3K-δ inhibitor (S = synergistic, A = additive, X = no effect).

Cell Line	**Indication**	**ED25**	**ED50**	**ED75**	**ED90**
Raji	Burkitt's	S	S	S	S
Ramos	Burkitt's	X	X	X	X
Daudi	Burkitt's	S	S	S	S
Mino	MCL	S	S	S	S
Pfeiffer	iNHL	S	S	S	S
DOHH	iNHL	S	S	S	S
REC-1	iNHL	S	S	A	A
U937	Myeloid	S	S	S	S
K562	CML	X	X	X	X
SU-DHL-1	ABC	S	A	X	X
SU-DHL-2	ABC	S	S	S	S
HBL-1	ABC	S	S	S	S
TMD8	ABC	S	S	S	S
LY19	GCB	X	X	X	X
LY7	GCB	S	S	S	S
LY1	GCB	X	X	X	X
SU-DHL-6	GCB	S	S	S	S
SupB15	B-ALL	S	S	S	S
CCRF	B-ALL	S	A/S	X	X

Example 3 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Orthotopic Pancreatic Cancer Model

[00301] An orthotopic pancreatic cancer model was used to investigate the therapeutic efficacy of the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) through treatment of the solid tumor microenvironment. Mice were dosed orally with 15 mg/kg of Formula (XVIII), 15 mg/kg of Formula (IX), or a combination of 15 mg/kg of both drugs.

[00302] Cell line derived from KrasG12D;Trp53R172H;Pdx1-Cre (KPC) mice were orthotopically implanted into the head of the pancreas after 35 passages. Based on the mice background from where the cell lines were generated, 1×10^6 cells were injected in C57BL/6 mice. Throughout the experiment, animals were provided with food and water ad libitum and subjected to a 12-h dark/light cycle. Animal studies were performed in accordance with the U.S. Public Health Service "Guidelines for the Care and Use of Laboratory Animals" (IACUC). After euthanization, pancreatic tumors were dissected out, weighed and single cell suspensions were prepared for flow cytometry analysis.

[00303] Results of the experiments are shown in FIG. 38, which illustrates tumor growth suppression in the orthotopic pancreatic cancer model. The statistical p-value (presumption against null hypothesis) is shown for each tested single agent and for the combination against the vehicle. The results show that all three treatments provide statistically significant reductions in tumor volume in the pancreatic cancer model.

[00304] Additional results of the experiments relating to treatment of the tumor microenvironment are shown in FIG. 39 to FIG. 41. FIG. 39 shows the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both drugs on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice. FIG. 40 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice. FIG. 41 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice. The results shown in FIG. 39 to FIG. 41 demonstrate that administration of the BTK inhibitor of Formula (XVIII) and the combination of the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) reduce immunosuppressive tumor associated myeloid cells and Tregs in pancreatic tumor-bearing mice. Overall, BTK inhibition with Formula (XVIII) or a combination of Formula (XVIII) and Formula (IX) significantly reduced tumor burden in an aggressive orthotopic PDA model, decreased immature myeloid infiltrate, reduced the number of tumor associated macrophages, and reduced the number of immunosuppressive Tregs, demonstrating a strong effect on the tumor microenvironment.

Example 4 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Ovarian Cancer Model

[00157] The ID8 syngeneic orthotropic ovarian cancer murine model was used to investigate the therapeutic efficacy of the BTK inhibitor of Formula (XVIII) through treatment of the solid tumor microenvironment. Human ovarian cancer models, including the ID8 syngeneic orthotropic ovarian cancer model and other animal models, are described in Fong and Kakar, *J. Ovarian Res.* **2009,** *2*, 12; Greenaway et al., *Gynecol. Oncol.* **2008,** *108,* 385-94; Urzua et al., *Tumour Biol.* **2005,** *26,* 236-44; Janat-Amsbury et al., *Anticancer Res.* **2006,** *26,* 3223-28; Janat-Amsbury et al., *Anticancer Res.* **2006,** *26,* 2785-89. Animals were treated with vehicle or Formula (XVIII), 15 mg/kg/BID given orally. The results of the study are shown in FIG. 42, FIG. 43, FIG. 44, FIG. 45, FIG. 46, FIG. 47, FIG. 48, and FIG.49.

[00158] FIG. 42 and FIG. 43 demonstrate that the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth in the ID8 syngeneic murine model. FIG. 44 shows that tumor response to treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor-associated lymphocytes in tumor-bearing mice. FIG. 45 shows treatment with the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth (through reduction in tumor volume) in the syngeneic murine model. FIG. 46 and FIG. 47 show that the tumor response induced by treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive B cells in tumor-bearing mice. FIG. 48 and FIG. 49 show that the tumor response induced by treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor associated Tregs and an increase in $CD8^+$ T cells.

[00159] The results shown in FIG. 42 to FIG. 49 illustrate the surprising efficacy of the BTK inhibitor of Formula (XVIII) in modulating tumor microenvironment in a model predictive of efficacy as a treatment for ovarian cancer in humans.

Example 5 – BTK Inhibitory Effects on Solid Tumor Microenvironment Through Modulation of Tumor-Infiltrating MDSCs and TAMs

[00160] A study was performed to observe potential reduction in tumor burden through modulation of tumor infiltrating MDSCs and TAMs using the BTK inhibitor of Formula (XVIII) and/or gemcitabine ("Gem"). In this study, KPC derived mouse pancreatic cancer cells (KrasG12D;Trp53R172H;Pdx1-Cre) were injected into the pancreases. Animals were treated with (1) vehicle; (2) Formula (XVIII), 15 mg/kg/BID given orally; (3) gemcitabine 15 mg/kg intravenous (IV) administered every 4 days for 3 injections; or (4) Formula (XVIII), 15 mg/kg/BID given orally with together with gemcitabine, 15 mg/kg IV administered every 4 days for 3 injections.

[00161] Single cell suspensions from tumor samples. Mouse tumor tissue was collected and stored in PBS/0.1% soybean trypsin inhibitor prior to enzymatic dissociation. Samples were finely minced with a scissors and mouse tissue was transferred into DMEM containing 1.0 mg/ml collagenase IV (Gibco), 0.1% soybean trypsin inhibitor, and 50 U/ml DNase (Roche) and incubated at 37C for 30 min. with constant stirring while human tissue was digested in 2.0 mg/ml collagenase IV, 1.0 mg/ml hyluronidase, 0.1% soybean trypsin inhibitor, and 50 U/ml DNase for 45 minutes. Suspensions were filtered through a 100 micron filter and washed with FACS buffer (PBS/0.5% BSA/2.0 mM EDTA) prior to staining. Two million total cells were stained with antibodies as indicated. Intracellular detection of FoxP3 was achieved following permeabilization with BD Perm Buffer III (BD Biosciences) and eBioscience Fix/Perm respectively. Following surface staining, samples were acquired on a BD Fortessa and analyzed using FlowJo (Treestar) software.

[00162] In FIG. 50, the reduction in tumor size upon treatment is shown. The effects on particular cell subsets are shown in the flow cytometry data presented in FIG. 51, FIG. 52, FIG. 53, and FIG. 54.

[00163] The results shown in FIG. 50 to FIG. 54 illustrate reduction in tumor burden by modulating the tumor infiltrating MDSCs and TAMs, which affects Treg and $CD8^-$ T cell levels, through inhibition of BTK using Formula (XVIII).

Example 6 – Effects of BTK Inhibitors on Thrombosis

[00164] Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit (Byrd, et al., *N. Engl. J. Med.* **2013**, *369(1),* 32-42, Wang, et al., *N. Engl. J. Med.* **2013,** *369(6),* 507-16). However, in these studies, bleeding has been reported in up to 50% of ibrutinib-treated patients. Most bleeding events were of grade 1-2 (spontaneous bruising or petechiae) but, in 5% of patients, they were of grade 3 or higher after trauma. These results are reflected in the prescribing information for ibrutinib, where bleeding events of any grade, including bruising and petechiae, were reported in approximately half of patients treated with ibrutinib (IMBRUVICA package insert and prescribing information, revised July 2014, U.S. Food and Drug Administration).

[00165] Constitutive or aberrant activation of the BCR signaling cascade has been implicated in the propagation and maintenance of a variety of B cell malignancies. Small molecule inhibitors of BTK, a protein early in this cascade and specifically expressed in B cells, have emerged as a new class of targeted agents. There are several BTK inhibitors, including Formula XXVII (CC-292), and Formula XX-A (PCI-32765, ibrutinib), in clinical development. Importantly, early stage clinical trials have found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), suggesting that this class of inhibitors may play a significant role in various types of cancers (Aalipour and Advani, *Br. J. Haematol.* **2013,** *163,* 436-43). However, their effects are not limited to leukemia or lymphomas as platelets also rely on the Tec kinases family members BTK and Tec for signal transduction in response to various thrombogenic stimuli (Oda, et al., *Blood* **2000**, *95(5),* 1663-70; Atkinson, et al. *Blood* **2003**, *102(10),* 3592-99). In fact, both Tec and BTK play an important role in the regulation of phospholipase Cγ2 (PLCγ2) downstream of the collagen receptor glycoprotein VI (GPVI) in human platelets. In addition, BTK is activated and undergoes tyrosine phosphorylation upon challenge of the platelet thrombin receptor, which requires the engagement of αIIbβ3 integrin and PI3K activity (Laffargue, et al., *FEBS Lett.* **1999,** *443(1),* 66-70). It has also been implicated in GPIbα-dependent thrombus stability at sites of vascular injury (Liu, et al., *Blood* **2006**, *108(8),* 2596-603). Thus, BTK and Tec are involved in several processes important in supporting the formation of a stable hemostatic plug, which is critical for preventing significant blood loss in response to vascular injury. Hence, the effects of the BTK inhibitor of Formula (XVIII) and ibrutinib were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus formation in the VWF HA1 mice model described in Chen et al. *Nat. Biotechnol.* **2008,** *26(1),* 114-19.

[00166] Administration of anesthesia, insertion of venous and arterial catheters, fluorescent labeling and administration of human platelets (5×10^8/ml), and surgical preparation of the cremaster muscle in mice have been previously described (Chen et al. *Nat Biotechnol.* **2008,** *26(1),* 114-19). Injury to the vessel wall of arterioles (~40–65 mm diameter) was performed using a pulsed nitrogen dye laser (440 nm, Photonic Instruments) applied through a 20× water-immersion Olympus objective (LUMPlanFl, 0.5 numerical aperature (NA)) of a Zeiss Axiotech vario microscope. Human platelet and wall interactions were visualized by fluorescence microscopy using a system equipped with a Yokogawa CSU-22 spinning disk confocal scanner, iXON EM camera, and 488 nm and 561 nm laser lines to detect BCECF-labeled and rhodamine-labeled platelets, respectively (Revolution XD, Andor Technology). The extent of thrombus formation was assessed for 2 min after injury and the area (μm^2) of coverage determined (Image IQ, Andor Technology). For the Formula (XVIII), Formula (XXVII) (CC-292), and Formula (XX-A) (ibrutinib) inhibition studies, the BTK inhibitors were were added to purified human platelets for 30 min before administration.

[00167] The *in vivo* throbus effects of the BTK inhibitors, Formula (XVIII), Formula (XXVII) (CC-292), and Formula (XX-A) (ibrutinib), were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus formation in the VWF HA1 mice model, which has been previously described (Chen et al. *Nat Biotechnol.* **2008,** *26(1),* 114-19). Purified human platelets were preincubated with various concentrations of the BTK inhibitors (0.1 μM, 0.5 μM, or 1 μM) or DMSO and then administered to VWF HA1 mice, followed by laser-induced thrombus formation. The BTK inhibitor-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Their behavior in response to laser-induced vascular injury was monitored in real time using two-channel confocal intravital microscopy (Furie and Furie, *J. Clin. Invest.* **2005,** *115(12),* 2255-62). Upon induction of arteriole injury untreated platelets rapidly formed thrombi with an average thrombus size of $6,450 \pm 292\ mm^2$ (mean ± s.e.m.), as shown in FIG. 55 and FIG. 56. Similarly, Formula (XVIII) (1 μM) treated platelets formed a slightly smaller but not significantly different thrombi with an average thrombus size of $5733 \pm 393\ mm^2$ (mean ± s.e.m.). In contrast, a dramatic reduction in thrombus size occured in platelets pretreated with 1 μM of Formula XX-A (ibrutinib), $2600 \pm 246\ mm^2$ (mean ± s.e.m.), resulting in a reduction in maximal thrombus size by approximately 61% compared with control ($P > 0.001$) (FIG. 55 and 57). Similar results were obtained with platelets pretreated with 500 nM of Formula (XVIII) or ibrutinib: thrombus size of $5946 \pm 283\ mm^2$, and $2710 \pm 325\ mm^2$ respectively. These initial results may provide some mechanic background and explaination on the reported 44% bleeding related adverse event rates in the Phase III RESONATE™ study comparing ibrutinib with ofatumumab. The results obtained for Formula XXVII (CC-292) were similar to that for Formula XX-A (ibrutinib), as shown in FIG. 55, 56, and 57. The effect of the BTK inhibitor concentration is shown in FIG. 58. These results demonstrate the surprising advantage of the BTK inhibitor of Formula (XVIII), which does not interfere with thrombus formation, while the BTK inhibitors of Formula XXVII (CC-292) and Formula XX-A (ibrutinib) interfere with thrombus formation.

[00168] The objective of this study was to evaluate *in vivo* thrombus formation in the presence of BTK inhibitors. *In vivo* testing of novel antiplatelet agents requires informative biomarkers. By utilizing a genetic modified mouse von Willebrand factor (VWFR1326H) model that supports human but not mouse platelet-mediated thrombosis, we evaluated the effects of Formula (XVIII), Formula XXVII (CC-292), and Formula XX-A (ibrutinib) on thrombus formation. These results show that Formula (XVIII) had no significant effect on human platelet-mediated thrombus formation while Formula XX-A (ibrutinib) was able to limit this process, resulting in a reduction in maximal thrombus size by 61% compared with control. Formula XXVII (CC-292) showed an effect similar to Formula XX-A (ibrutinib). These results, which show reduced thrombus formation for ibrutinib at physiologically relevant concentrations, may provide some mechanistic background for the Grade ≥ 3 bleeding events (eg, subdural hematoma, gastrointestinal bleeding, hematuria and postprocedural hemorrhage) that have been reported in ≤ 6% of patients treated with Formula XX-A (ibrutinib).

[00169] GPVI platelet aggregation was measured for Formula (XVIII) and Formula XX-A (ibrutinib). Blood was obtained from untreated humans, and platelets were purified from plasma-rich protein by centrifugation. Cells were resuspended to a final concentration of 350,000/µL in buffer containing 145 mmol/L NaCl, 10 mmol/L HEPES, 0.5 mmol/L Na_2HPO_4, 5 mmol/L KCl, 2 mmol/L $MgCl_2$, 1 mmol/L $CaCl_2$, and 0.1% glucose, at pH 7.4. Stock solutions of Convulxin (CVX) GPVI were prepared on the day of experimentation and added to platelet suspensions 5 minutes (37 °C, 1200 rpm) before the induction of aggregation. Aggregation was assessed with a Chronolog Lumi-Aggregometer (model 540 VS; Chronolog, Havertown, PA) and permitted to proceed for 6 minutes after the addition of agonist. The results are reported as maximum percent change in light transmittance from baseline with platelet buffer used as a reference. The results are shown in FIG. 59.

[00170] In FIG. 60, the results of CVX-induced (250 ng/mL) human platelet aggregation results before and 15 min after administration of the BTK inhibitors to 6 healthy individuals are shown.

[00171] The results depicted in FIG. 59 and FIG. 60 indicate that the BTK inhibitor of Formula XX-A (ibrutinib) significantly inhibits GPVI platelet aggregation, while the BTK inhibitor of Formula (XVIII) does not, further illustrating the surprising benefits of the latter compound.

Example 7 – Study of a BTK Inhibitor and a Combination of a BTK Inhibitor and a PI3K Inhibitor in Canine Lymphoma

[00172] Canine B cell lymphoma exists as a pathological entity that is characterized by large anaplastic, centroblastic or immunoblastic lymphocytes with high proliferative grade, significant peripheral lymphadenopathy and an aggressive clinical course. While some dogs respond initially to prednisone, most canine lymphomas progress quickly and must be treated with combination therapies, including cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP), or other cytotoxic agents. In their histopathologic features, clinical course, and high relapse rate after initial treatment, canine B cell lymphomas resemble diffuse large B cell lymphoma (DLBCL) in humans. Thus, responses of canine B cell lymphomas to experimental treatments are considered to provide proof of concept for therapeutic candidates in DLBCL.

[00173] In this example, companion dogs with newly diagnosed or relapsed/refractory LSA were enrolled on a veterinary clinical trial of the BTK inhibitor of Formula (XVIII) ("Arm 1") or the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) ("Arm 2"). Enrollment has completed for Arm 1 and is ongoing for Arm 2. With approximately 1/3 of Arm 2 subjects treated, the preliminary results show that combined treatment with the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) may have greater efficacy than treatment with the BTK inhibitor of Formula (XVIII) alone in aggressive lymphoma.

[00174] Twenty-one dogs were treated in Arm 1 with the BTK inhibitor of Formula (XVIII) at dosages of 2.5 mg/kg once daily to 20 mg/kg twice daily. Intra-subject dose escalation was allowed. Six of the 11 dogs that initiated at 2.5 or 5 mg/kg once daily were escalated and completed the study with dosages of 10 mg/kg twice daily. Among all the dose cohorts, 8 dogs had shrinkage of target lesions >20%; the best tumor responses were between 45-49% reduction in the sum of target lesions in two dogs. Complete responses ("CR", disappearance of all evidence of disease per evaluator judgment; and absence of new lesions) were not observed in Arm 1.

[00175] In the combination phase of the study (Arm 2), 7 dogs have been treated with 10 mg/kg the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) at 2.5 or 3.5 mg/kg, on a twice daily schedule. To date, 4 dogs had shrinkage of target lesions > 20%; and the best tumor responses were between 58-65% reduction in the sum of target lesions, with one sustained CR observed. Initial reductions in the sum of target lesions were observed to deepen during the course of therapy in 4 of the 7 dogs. A summary of the results is presented in Table 5.

TABLE 5. Summary of the results of the canine lymphoma study.

Response Metric	**Formula (XVIII) and Formula (IX)[a]**	**Formula (XVIII) monotherapy**
Sum LD[b] decreased by ≥20%	4/7 (57.1 %)	8/21 (38.1 %)
Sum LD[b] decreased by ≥30% (PR)	2/7 (28.6 %)	6/21 (28.6 %)
CR by investigator evaluation	1/7 (14.3 %)	0/21
Median time on study (all subjects)	25 days	24 days
Median time to best response	21 days	7 days

[a] Arm 2 is still recruiting subjects

[b] LD, longest diameter of up to 5 target lesion

[00305] These preliminary data suggest that in companion dogs with naturally occurring B cell lymphomas, treatment with the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) may provide increased biological activity (tumor shrinkage and stable disease) and may possibly lead to deeper responses than treatment with the BTK inhibitor of Formula (XVIII) alone. Although the available data represent only 1/3 of the planned Arm 2 population, the extended response time (median time to best response) and observation of a CR among the few dogs treated to date may be evidence of synergy between Formula (XVIII) and Formula (IX) in this highly aggressive disease.

CLAIMS

We claim:

1. A method of treating a hyperproliferative disorder in a subject, comprising co-administering to a subject in need thereof a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor, or of a pharmaceutically acceptable salt thereof, in combination with a Bruton's tyrosine kinase (BTK) inhibitor, or of a pharmaceutically acceptable salt thereof.

2. The method of Claim 1, wherein the PI3K inhibitor is selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor.

3. The method of claim 2, wherein the PI3K inhibitor is a PI3K-γ,δ inhibitor.

4. The method of any one of claims 1 to 3, wherein the hyperproiferative disorder is leukemia, lymphoma, or a solid tumor cancer.

5. The method of any one of Claims 1 to 4, wherein the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers.

6. The method of any one of Claims 1 to 5, wherein the combination of the PI3K inhibitor with the BTK inhibitor is administered by oral, intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

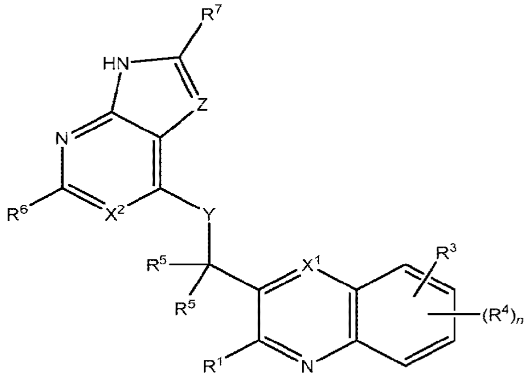
7. The method of any one of Claims 1 to 6, wherein the PI3K inhibitor and/or BTK inhibitor is in the form of a pharmaceutically acceptable salt.

8. The method of any one of Claims 1 to 7, wherein the PI3K inhibitor is administered to the subject before administration of the BTK inhibitor.

9. The method of any one of Claims 1 to 7, wherein the PI3K inhibitor is administered concurrently with the administration of the BTK inhibitor.

10. The method of any one of Claims 1 to 7, wherein the PI3K inhibitor is administered to the subject after administration of the BTK inhibitor.

11. The method of any one of Claims 1 to 10, wherein the PI3K inhibitor is:



or a pharmaceutically-acceptable salt thereof, wherein:

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

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

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

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one 0 or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1_4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}, $N(C_{1-4}$alkyl)C_{1-4}alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$. —$OC(=O)N(R^a)S(=O)_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, $OS(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —

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

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

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

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

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

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

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

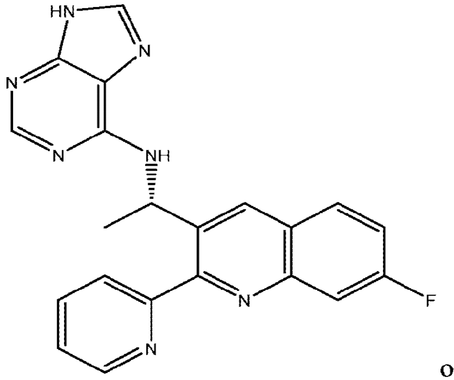
R^9 is selected from H, halo, C$_{1-4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^{a}C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2-6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a,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

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

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

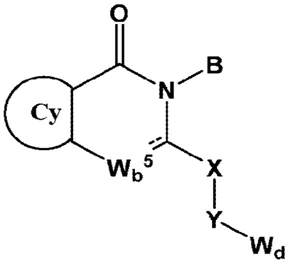
R^a is independently, at each instance, H or R^b; and R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6} alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3} haloalkyl, —OC_{1-4}alkyl, —NH_2, —NHC_{1-4}alkyl,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

12. The method of Claim 11, wherein the PI3K inhibitor is:



or a pharmaceutically acceptable salt thereof.

13. The method of any one of Claims 1 to 10, wherein the PI3K inhibitor is:



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

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

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

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

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

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

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

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

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

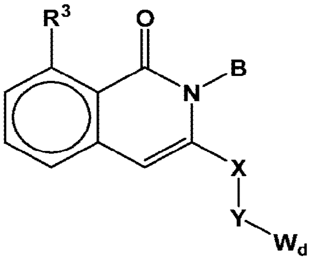
each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

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

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

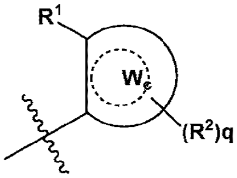
R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate,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

14. The method of Claim 13, wherein the PI3K inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

B is:



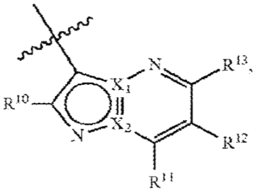
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

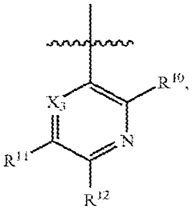
q is an integer of 0, 1, 2, 3, or 4;

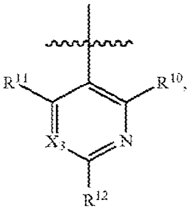
X is a bond or $-(CH(R^9))_z-$, and z is an integer of 1;

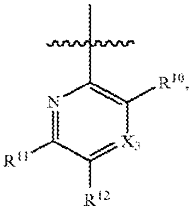
Y is $-N(R^9)-$;

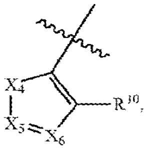
W_d is:

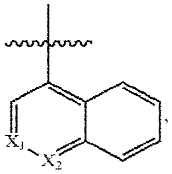

R10
X1
X2
N
N
R13,
R12
R11

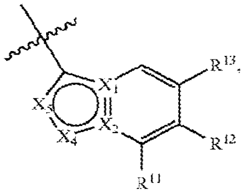

X3
R10,
N
R11
R12

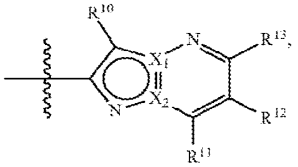

R11
R10,
X3
N
R12

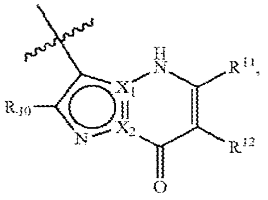

N
R10,
X3
R11
R12


X4
R10,
X5
X6

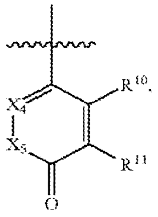

X1
X2


X5
X1
X2
X4
R13,
R12
R11

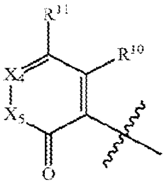

R10
X1
X2
N
N
R13,
R12
R11



H
N
R^{11},
X_1
R_{10}
X_2
N
R^{12}
O

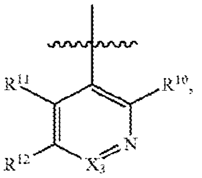


X_4
R^{10},
X_5
R^{11}
O

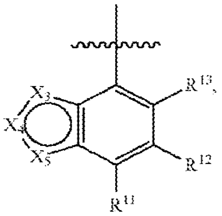


R^{11}
X_4
R^{10}
X_5
O

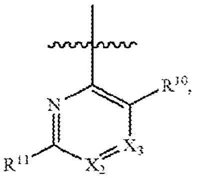
,



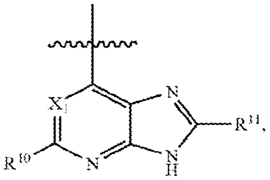
R^{11}
R^{10},
N
R^{12}
X_3



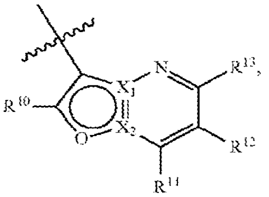
X_3
R^{13},
X_4
X_5
R^{12}
R^{11}



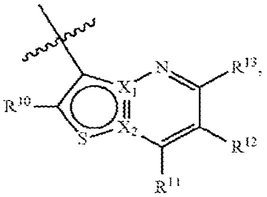
N
R^{10},
X_3
R^{11}
X_2



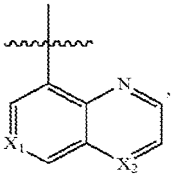
X_1
N
R^{11},
R^{10}
N
N
H



N
R^{13},
X_1
R^{10}
O
X_2
R^{12}
R^{11}

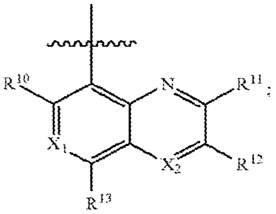


N
R^{13},
X_1
R^{10}
S
X_2
R^{12}
R^{11}



N
X_1
X_2

, or



R^{10}
N
R^{11};
X_1
X_2
R^{12}
R^{13}

;

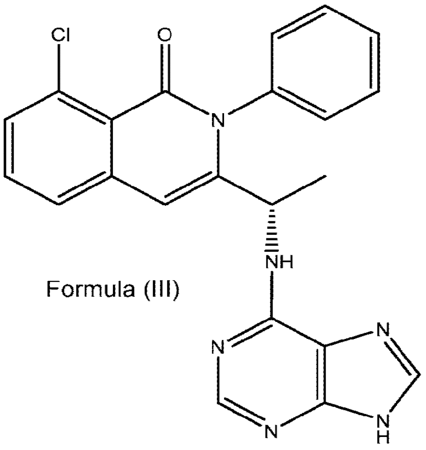
X_1, X_2 and X_3 are each independently C, CR^{13} or N; and X_4, X_5 and X_6 are each independently N, NH, CR^{13}, S or O;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy or nitro; and

each instance of R^9 is independently hydrogen, alkyl, or heterocycloalkyl.

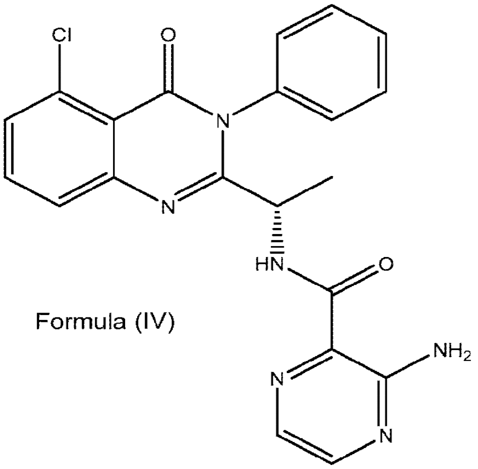
15. The method of Claim 14, wherein the PI3K inhibitor is



Formula (III)

or a pharmaceutically acceptable salt thereof.

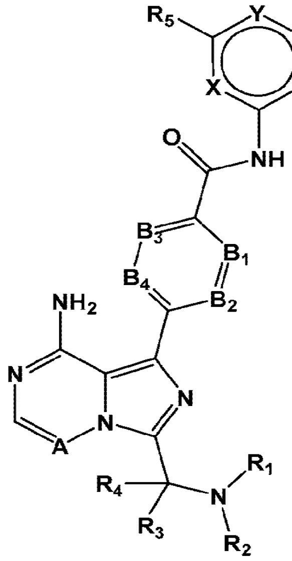
16. The method of Claim 14, wherein the PI3K inhibitor is



Formula (IV)

or a pharmaceutically acceptable salt thereof.

17. The method of any one of Claims 1 to 10, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

X is CH, N, O or S;

Y is $C(R_6)$, N, O or S;

Z is CH, N or bond;

A is CH or N;

B_1 is N or C(R_7);

B_2 is N or C(R_8);

B_3 is N or C(R_9);

B_4 is N or C(R_{10});

R_1 is R_{11}C(O), R_{12}S(O), $R_{13}SO_2$ or (1-6C)alkyl optionally substituted with R_{14};

R_2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R_3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R_2 and R_3 form, together with the N and C atom they are attached to, a (3- 7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R_4 is H or (1-3C)alkyl;

R_5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R_5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R_6 is H or (1-3C)alkyl; or

R_5 and R_6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R_7 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy;

R_8 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy; or

R_7 and R_8 together with the carbon atoms they are attached to, form (6-10C)aryl or (1-9C)heteroaryl;

R_9 is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{10} is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{11} is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or R_{11} is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

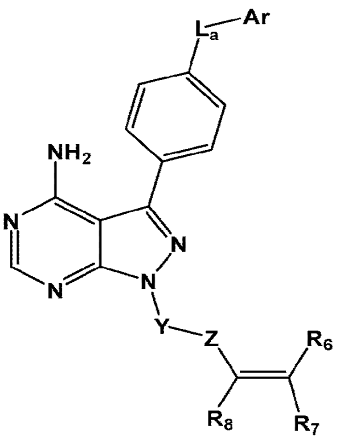
R_{11} is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R_{12} and R_{13} are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

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

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

18. The method of any one of Claims 1 to 10, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

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

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

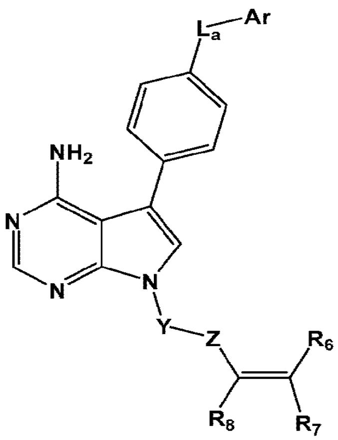
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

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

R_6 is H; and

R is H or C_1-C_6alkyl.

19. The method of any one of Claims 1 to 10, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

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

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

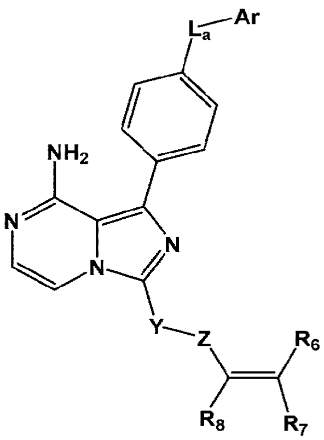
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

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

R_6 is H; and

R is H or C_1-C_6alkyl.

20. The method of any one of Claims 1 to 10, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

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

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

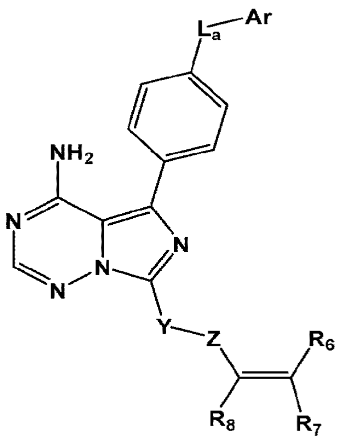
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

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

R_6 is H; and

R is H or C_1-C_6alkyl.

21. The method of any one of Claims 1 to 10, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

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

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

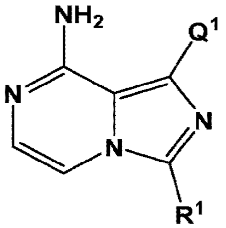
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

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

R_6 is H; and

R is H or C_1-C_6alkyl.

22. The method of any one of Claims 1 to 10, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof,

wherein:

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

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

G^1 and G^{41} are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, -CN, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C{=}O)R^3$, $NR^2(C{=}O)OR^3$, $NR^2(C{=}O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C{=}S)OR^2$, $-(C{=}O)SR^2$, $-NR^2(C{=}NR^3)NR^{2a}R^{3a}$, $-NR^2(C{=}NR^3)OR^{2a}$, $-NR^2(C{=}NR^3)SR^{3a}$, $-O(C{=}O)OR^2$, $-O(C{=}O)NR^2R^3$, $-O(C{=}O)SR^2$, $-S(C{=}O)OR^2$, $-S(C{=}O)NR^2R^3$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333}a)_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333a}$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents; or $-(X^1)_n-(Y^1)_m-R^4$; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333a}$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, -CF$_3$, -OCF$_3$, -OR^{222}, -NR^{222}, R^{333}(R^{333a})$_{j3a}$, -C(O)R^{222}, -CO$_2$R^{222}, -CONR^{222}R^{333}, -NO$_2$, -CN, -S(O)$_{j3a}$R^{222}, -SO$_2$NR^{222}R^{333}, NR^{222}(C=O)R^{333}, NR^{222}(C=O)OR^{333}, NR^{222}(C=O)NR^{222}R^{333}, NR^{222}S(O)$_{j3a}$R^{333}, -(C=S)OR^{222}, -(C=O)SR^{222}, -NR^{222}(C=NR^{333})NR^{222}aR^{333}a, -NR^{222}(C=NR^{333})OR^{222a}, -NR^{222}(C=NR^{333})SR^{333}a, -O(C=O)OR^{222}, -O(C=O)NR^{222}R^{333}, -O(C=O)SR^{222}, -S(C=O)OR^{222}, or -S(C=O)NR^{222}R^{333} substituents;

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

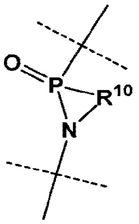
$NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j6a}R^{3331}$, $-(C=S)OR^{2221}$, $-(C=O)SR^{2221}$, $-NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C=NR^{3331})OR^{222a1}$, $-NR^{2221}(C=NR^{3331})SR^{333a1}$, $-O(C=O)OR^{2221}$, $-O(C=O)NR^{2221}R^{3331}$, $-O(C=O)SR^{2221}$, $-S(C=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C=O)NR^{2221}R^{3331}$ substituents; or G^{11} is taken together with the carbon to which it is attached to form a double bond which is substituted with R^5 and G^{111};

R^2, R^{2a}, R^3, R^{3a}, R^{222}, R^{222}a, R^{333}, R^{333a}, R^{21}, R^{2a1}, R^{31}, R^{3a1}, R^{2221}, R^{222a1}, R^{3331}, and R^{333a1} are each independently equal to C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or in the case of $-NR^2R^3(R^{3a})_{j1}$ or $-NR^{222}R^{333}(R^{333}a)_{j1}a$ or $-NR^{222}R^{333}(R^{333}a)j2a$ or $-NR^{2221}R^{3331}(R^{333a1})_{j3a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, R^2 and R^3 or R^{222} and $R^{333}3$ or R^{2221} and R^{3331} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted by one or more G^{111} substituents;

X^1 and Y^1 are each independently $-O-$, $-NR^7-$, $-S(O)_{j7}-$, $-CR^5R^6-$, $-N(C(O)OR^7)-$, $-N(C(O)R^7)-$, $-N(SO_2R^7)-$, $-CH_2O-$, $-CH_2S-$, $-CH_2N(R^7)-$, $-CH(NR^7)-$, $-CH_2N(C(O)R^7)-$, $-CH_2N(C(O)OR^7)-$, $-CH_2N(SO_2R^7)-$, $-CH(NHR^7)-$, $-CH(NHC(O)R^7)-$, $-CH(NHSO_2R^7)-$, $-CH(NHC(O)OR^7)-$, $-CH(OC(O)R^7)-$, $-CH(OC(O)NHR^7)-$, $-CH=CH-$, -C.ident.C-, $-C(=NOR^7)-$, $-C(O)-$, $-CH(OR^7)-$, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$ $-OC(O)N(R^7)-$, $-N(R^7)C(O)N(R^7)-$, $-NR^7C(O)O-$, $-S(O)N(R^7)-$, $-S(O)_2N(R^7)-$, $-N(C(O)R^7)S(O)-$, $-N(C(O)R^7)S(O)_2-$, $-N(R^7)S(O)N(R^7)-$, $-N(R^7)S(O)_2N(R^7)-$, $-C(O)N(R^7)C(O)-$, $-S(O)N(R^7)C(O)-$, $-S(O)_2N(R^7)C(O)-$, $-OS(O)N(R^7)-$, $-OS(O)_2N(R^7)-$, $-N(R^7)S(O)O-$, $-N(R^7)S(O)_2O-$, $-N(R^7)S(O)C(O)-$, $-N(R^7)S(O)_2C(O)-$, $-SON(C(O)R^7)-$, $-SO_2N(C(O)R^7)-$, $-N(R^7)SON(R^7)-$, $-N(R^7)SO_2N(R^7)-$,

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

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



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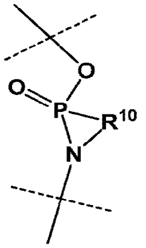

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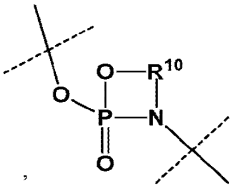

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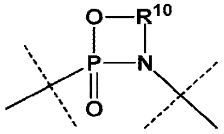

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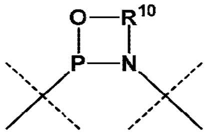
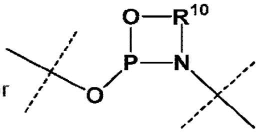


or



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

R^5, R^6, and G^{111} are each independently a C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}R^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R^{69}; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R^{69};

R^7 and R^8 are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G^{111} substituents;

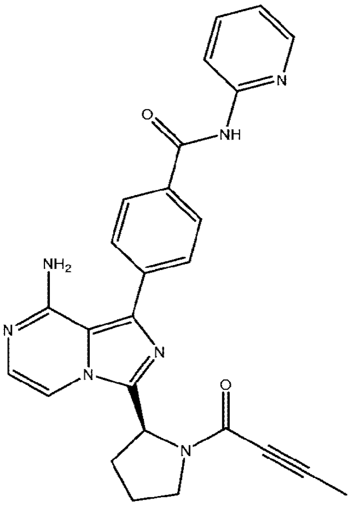
R^4 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G^{41} substituents;

R^{69} is equal to halo, $-OR^{78}$, -SH, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-CONR^{78}R^{88}$, $-NO_2$, -CN, $-S(O)_{j8}R^{78}$, $-SO_2NR^{78}R^{88}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or -N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$ $SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

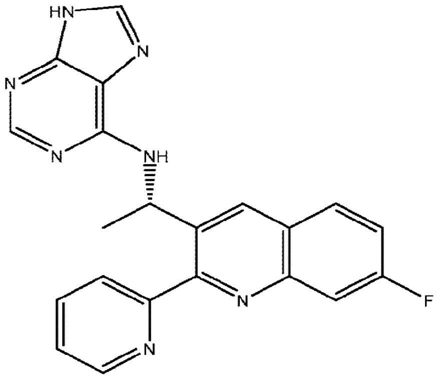
R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl,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

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

23. The method of any one of Claims 1 to 10, wherein the BTK inhibitor is:



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



or a pharmaceutically-acceptable salt thereof.

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

25. The method of any one of claims 1 to 23, which is a method of treating a cancer in a

human comprising administering a therapeutically effective dose of a BTK inhibitor and a PI3K inhibitor in combination, wherein the dose is effective to inhibit signaling between the cells of the cancer and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts.

26. The method of Claim 24, wherein the cancer is a solid tumor cancer.

27. The method of Claim 25, wherein the solid tumor cancer is selected from the group consisting of colon carcinoma, pancreatic carcinoma, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, and stomach cancer.

28. The method of any one of Claims 24-26, wherein the dose is further effective to increase immune system recognition and rejection of the cancer by the human.

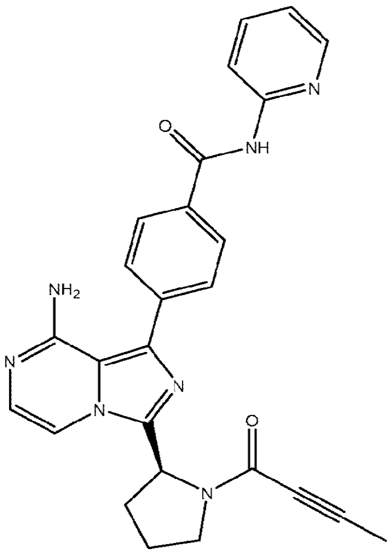
29. A PI3K inhibitor and a BTK inhibitor in combination, for use in treating a hyperproliferative disorder.

30. A pharmaceutical composition comprising a PI3K inhibitor and a BTK inhibitor in combination, and at least one pharmaceutically acceptable excipient.

31. The pharmaceutical composition of claim 29, for use in treating a hyperproliferative disorder.

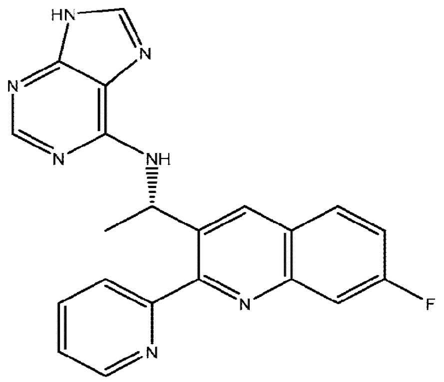
32. A kit comprising a pharmaceutical composition comprising a PI3K inhibitor and a pharmaceutical composition comprising a BTK inhibitor, for co-administration of the PI3K inhibitor and the BTK inhibitor, either simultaneously or separately.

33. A method of treating a cancer in a human sensitive to platelet-mediated thrombosis comprising the step of administering a therapeutically effective dose of a PI3K inhibitor and a BTK inhibitor, wherein the BTK inhibitor is:



or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

34. The method of Claim 32, wherein the PI3K inhibitor is:



or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

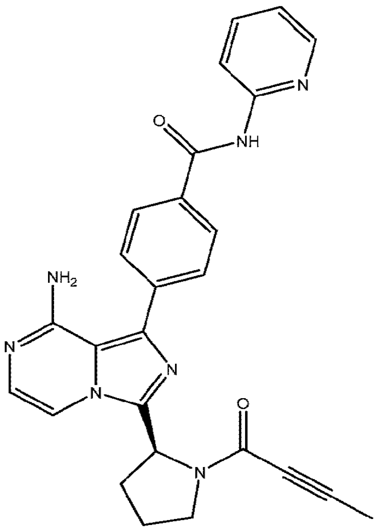
35. The method of any of Claims 32-33, further comprising the step of administering a therapeutically effective dose of an anticoagulent or antiplatelet agent.

36. The method of Claim 34, wherein the anticoagulent or antiplatelet agent is selected from the group consisting of clopidogrel, prasugrel, ticagrelor, ticlopidine, warfarin,

acenocoumarol, dicumarol, phenprocoumon, heparain, low molecular weight heparin, fondaparinux, and idraparinux.

37. The method of any of Claims 32-35, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired immune deficiency syndrome (AIDS)-related cancer, viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hogkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

38. A method of treating a cancer in a human with a history of thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is:



or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: PCT/US14/68938 Document Date: 12/05/2014

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 055112-5002-WO

Box No. I TITLE OF INVENTION

Therapeutic Combination of a PI3K Inhibitor and a BTK Inhibitor

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Acerta Pharma B.V.
Pivot Park Room RK 2111
Molenweg 79
5349 AC Oss, The Netherlands

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☐ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address:

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of: ☒ all designated States ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VOGT, Frederick G.
Morgan Lewis & Bockius LLP
1701 Market Street
Philadelphia, Pennsylvania 19103
United States of America

Telephone No. 215-963-4608

Facsimile No. 215-963-5001

Agent's registration No. with the Office 70115

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☒ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address: phpatentcorrespondence@morganlewis.com

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Form PCT/RO/101 (first sheet) (16 September 2012) *See Notes to the request form*

Sheet No. 2

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HAMDY, Ahmed
640 Henry Cowell Drive
Santa Cruz, California 95060
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ROTHBAUM, Wayne
101 Central Park West, PHC
New York, New York 10023
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

IZUMI, Raquel
3437 Brittan Avenue
San Carlos, California 94070
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LANNUTTI, Brian
627 Glencrest Place
Solana Beach, California 92075
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Form PCT/RO/101 (continuation sheet) (16 September 2012) *See Notes to the request form*

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COVEY, Todd
3437 Brittan Avenue
San Carlos, California 94070
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ULRICH, Roger
22525 SE 46th Place
Sammamish, Washington 98075
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

JOHNSON, Dave
4442 54th Avenue SW
Seattle, Washington 98116
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BARF, Tjeerd
St. Luciastraat 7
5371 AS, Ravenstein
The Netherlands

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Sheet No. . . . 4 . .

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KAPTEIN, Allard
Nonnenstraat 14
5301 BJ, Zaltmommel
The Netherlands

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, ***the space is insufficient*** *to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

- *(i)* ***if more than one person is to be indicated as applicant and/or inventor*** *and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*
- *(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication* ***"the States indicated in the Supplemental Box"*** *is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
- *(iii) if, in Box No. II or in any of the sub-boxes of Box No. III,* ***the inventor or the inventor/applicant is not inventor for the purposes of all designated States****: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
- *(iv) if, in addition to the agent(s) indicated in Box No. IV, there are* ***further agents****: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
- *(v) if, in Box No. VI, there are* ***more than three earlier applications whose priority is claimed****: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

*2. If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such case, write the name or two-letter code of each designated State concerned and the indication "****patent of addition,****" "****certificate of addition,****" "****inventor's certificate of addition****" or "****utility certificate of addition,****" the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other parent grant or the date of filing of the parent application (Rules 4.11(a)(i) and 49bis.1(a) or (b)).*

*3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such case, write "United States of America" or "US" and the indication "****continuation****" or "****continuation-in-part****" and the number and the filing date of the parent application (Rules 4.11(a)(ii) and 49bis.1(d)).*

Continuation of Box IV:

BEARDELL, Jr., Louis W., Reg. No. 40,506
HALLIDAY, Christopher I., Reg. No. 42,621
DAVIS, Kenneth J., Reg. No. 50,688
MCCULLEN, Sharon B., 54,303
VIRELLI, Jr., Louis J., Reg. No. 26,818
WEISBERG, Alison B., Reg. No. 45,206
KOLESAR, Dana, Reg. No. 55,338
HEMMER, John L., Reg. No. 58,752
UDAL, Robert P., Reg. No. 56,608
LEUNG, Richard L., Reg. No. 60,711
RYAN, Michael, Reg. No. 63,115
SERVANCE, Squire J., Reg. No. 65,135
VOGT, Frederick G., Reg. No. 70,115
LEACH, Justine, Reg. No. 58,957
PATHAK, Shantanu, Reg. No. 65,585
(All of the above attorneys and/or patent agents are members of Morgan Lewis & Bockius LLP (Contact information for all is listed in Box IV))

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a) the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection

☐ JP Japan **is not designated** for any kind of national protection

☐ KR Republic of Korea **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM AND DOCUMENT

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 05 December 2013 (05.12.2013)	61/912,515	US		
item (2) 03 April 2014 (03.04.2014)	61/974,665	US		
item (3) 11 August 2014 (11.08.2014)	62/035,777	US		

☐ Further priority claims are indicated in the Supplemental Box.

Furnishing the priority document(s):

☒ The **receiving Office** is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application(s) was filed with the receiving Office which, for the purposes of this international application, is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

☐ The **International Bureau** is requested to obtain from a digital library a certified copy of the earlier application(s) identified above, using, where applicable, the access code(s) indicated below *(if the earlier application(s) is available to it from a digital library)*:

☐ item (1) access code ______________ ☐ item (2) access code ______________ ☐ item (3) access code ______________ ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (______________________________). *(See also the Notes to Box No. VI; further information **must** be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if more than one International Searching Authority is competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA/ EP

See Notes to the request form

Box No. IX **CHECK LIST for EFS-Web filings** - this sheet is only to be used when filing an international application with RO/US via **EFS-Web**

This international application **contains** the following:	Number of sheets
(a) request form PCT/RO/101 (including any declarations and supplemental sheets) .... :	7
(b) description (excluding any sequence listing part of the description, see (f), below) ..... :	147
(c) claims .... :	29
(d) abstract .... :	1
(e) drawings (if any) .... :	60
(f) sequence listing part of the description in the form of an **image file** (e.g. PDF).......... :	
Total number of sheets (including the sequence listing part of the description if **filed as an image file**) .... :	244

(g) sequence listing part of the description

☐ filed in the form of an **Annex C/ST.25 text file**

☐ WILL BE filed separately on physical data carrier(s), on the same day and in the form of an **Annex C/ST.25 text file**

Indicate type and number of physical data carrier(s) ....

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item):*	Number of items
1. ☒ fee calculation sheet .... :	1
2. ☐ original separate power of attorney .... :	
3. ☐ original general power of attorney .... :	
4. ☐ copy of general power of attorney; reference number:.......... .... :	
5. ☐ priority document(s) identified in Box No. VI as item(s) .... :	
6. ☐ Translation of international application into *(language)*: .... :	
7. ☐ separate indications concerning deposited microorganism or other biological material .... :	
8. ☐ *(only where item (f) is marked in the left column)* copy of the sequence listing in electronic form (Annex C/ST.25 text file) not forming part of the international application but **furnished only for the purposes of international search** under Rule 13*ter*.............. :	
9. ☐ *(only where item (f) is marked in the left column)* a statement confirming that "the information recorded in electronic form submitted under Rule 13*ter* is identical to the sequence listing as contained in the international application" as filed via EFS-Web: .... :	
10. ☐ copy of results of earlier search(es) (Rule 12*bis*.1(a)) .. :	
11. ☐ other *(specify)*:................................ :	

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: English

Box No. X **SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

/Frederick G. Vogt/

Frederick G. Vogt, PTO Regis. No. 70115

For receiving Office use only

1. Date of actual receipt of the purported international application: 05 DEC 2014 (05.12.14)

2. Drawings:

☐ received:

☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Form PCT/RO/101 (last sheet – EFS) (16 September 2012) *See Notes to the request form*

WIPO
WORLD
INTELLECTUAL PROPERTY
ORGANIZATION

DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/IB2015/000645**
International filing date:		**21 January 2015 (21.01.2015)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**US**
	Number:	**PCT/US2014/068938**
	Filing date:	**05 December 2014 (05.12.2014)**
Date of receipt at the International Bureau:		**09 February 2015 (09.02.2015)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

34, chemin des Colombettes
1211 Geneva 20, Switzerland
www.wipo.int

SEQUENCE LISTINGS

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<120>  METHODS OF TREATING CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL
       LYMPHOCYTIC LEUKEMIA USING A BTK INHIBITOR

<130>  055112-5004-WO

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Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
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Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
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Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335
```

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
        355                 360                 365


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445


Pro Gly Lys
    450


<210>  2
<211>  213
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Light chain amino acid sequence of the anti-CD20 monoclonal
       antibody rituximab.

<400>  2

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1               5                   10                  15


Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30


His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45
```

```
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80


Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205


Asn Arg Gly Glu Cys
    210


<210>  3
<211>  449
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Heavy chain amino acid sequence of the anti-CD20 monoclonal
       antibody obinutuzumab.

<400>  3
```

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Tyr Ser
            20                  25                  30

Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Arg Ile Phe Pro Gly Asp Gly Asp Thr Asp Tyr Asn Gly Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Val Phe Asp Gly Tyr Trp Leu Val Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220
```

```
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
```

```
Lys


<210>  4
<211>  219
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Light chain amino acid sequence of the anti-CD20 monoclonal
       antibody obinutuzumab.

<400>  4

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Ile Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Val Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Asn
                85                  90                  95


Leu Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
```

```
                165                 170                 175


Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  5
<211>  122
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Variable heavy chain amino acid sequence of the anti-CD20
       monoclonal antibody ofatumumab.

<400>  5

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
            20                  25                  30


Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95


Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110


Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

```
<210>  6
<211>  107
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Variable light chain amino acid sequence of the anti-CD20
       monoclonal antibody ofatumumab.

<400>  6

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
                85                  90                  95


Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105


<210>  7
<211>  222
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab fragment of heavy chain amino acid sequence of the anti-CD20
       monoclonal antibody ofatumumab.

<400>  7

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Gly Ser Ser Lys Ser Thr Ser Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
    210                 215                 220

<210>  8
<211>  211
<212>  PRT
<213>  Artificial Sequence
```

```
<220>
<223>  Fab fragment of light chain amino acid sequence of the anti-CD20
       monoclonal antibody ofatumumab.

<400>  8

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
                85                  90                  95


Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
```

```
        195                 200                 205


Phe Asn Arg
    210


<210>  9
<211>  451
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Heavy chain amino acid sequence of the anti-CD20 monoclonal
       antibody veltuzumab.

<400>  9

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Asn Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Tyr Pro Gly Met Gly Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Phe Tyr Tyr Cys
                85                  90                  95


Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125


Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140


Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
```

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445


Pro Gly Lys
    450


<210>  10
<211>  213
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Light chain amino acid sequence of the anti-CD20 monoclonal
       antibody veltuzumab.

<400>  10

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30


His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Pro Trp Ile Tyr
        35                  40                  45


Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80


Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95
```

```
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205


Asn Arg Gly Glu Cys
    210


<210>  11
<211>  447
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Heavy chain amino acid sequence of the anti-CD20 monoclonal
       antibody tositumomab.

<400>  11

Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Asn Met His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Val Val Tyr Tyr Ser Asn Ser Tyr Trp Tyr Phe Asp Val Trp
            100                 105                 110

Gly Thr Gly Thr Thr Val Thr Val Ser Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270
```

```
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210>  12
<211>  210
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Light chain amino acid sequence of the anti-CD20 monoclonal
       antibody tositumomab.

<400>  12

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
```

```
1               5                   10                  15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

Ala Pro Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
                85                  90                  95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg
    210

<210>  13
```

```
<211>  443
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Heavy chain amino acid sequence of the anti-CD20 monoclonal
       antibody ibritumomab.

<400>  13

Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Asn Met His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80


Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Val Val Tyr Tyr Ser Asn Ser Tyr Trp Tyr Phe Asp Val Trp
            100                 105                 110


Gly Thr Gly Thr Thr Val Thr Val Ser Ala Pro Ser Val Tyr Pro Leu
        115                 120                 125


Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys
    130                 135                 140


Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn Ser
145                 150                 155                 160


Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175


Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp
            180                 185                 190
```

```
Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr
        195                 200                 205

Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys
    210                 215                 220

Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser
                245                 250                 255

Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp
            260                 265                 270

Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln
        275                 280                 285

Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser
    290                 295                 300

Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys
305                 310                 315                 320

Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile
                325                 330                 335

Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro
            340                 345                 350

Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met
        355                 360                 365

Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn
    370                 375                 380

Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn
                405                 410                 415
```

```
Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu
            420                 425                 430


His Asn His His Thr Thr Lys Ser Phe Ser Arg
        435                 440


<210>  14
<211>  209
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Light chain amino acid sequence of the anti-CD20 monoclonal
       antibody ibritumomab.

<400>  14

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1               5                   10                  15


Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30


His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45


Ala Pro Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80


Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
                85                  90                  95


Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
            100                 105                 110


Thr Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140
```

```
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn
```

683621

THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

February 08, 2015

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APPLICATION NUMBER: *62/035,777*
FILING DATE: *August 11, 2014*
RELATED PCT APPLICATION NUMBER: *PCT/US15/12288*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US62/035,777*

Certified by

David J. Kappos

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

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Inventor 2					Remove
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Raquel		Izumi	San Carlos	CA	US
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Given Name	Middle Name	Family Name	City	State	Country i
Dave		Johnson	Seattle	WA	US
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Given Name	Middle Name	Family Name	City	State	Country i
Tjeerd		Barf	Ravenstein		NL

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Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

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Inventor 9				Remove	
Given Name	Middle Name	Family Name	City	State	Country i
Allard		Kaptein	Zaltmommel		NL

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Title of Invention	Therapeutic Combination of a PI3K Inhibitor and a BTK Inhibitor
Attorney Docket Number (if applicable)	055112-5002-02-PR

Correspondence Address

Direct all correspondence to (select one):

● The address corresponding to Customer Number	○ Firm or Individual Name
Customer Number	28977

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

● No.

○ Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:

○ Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
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Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

○ Applicant asserts small entity status under 37 CFR 1.27

○ Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.

● No

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Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Frederick G. Vogt/			Date (YYYY-MM-DD)	2014-08-11
First Name	Frederick G.	Last Name	Vogt	Registration Number (If appropriate)	70115

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6. A record in this system of records may be disclosed, as a routine use, to an other federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

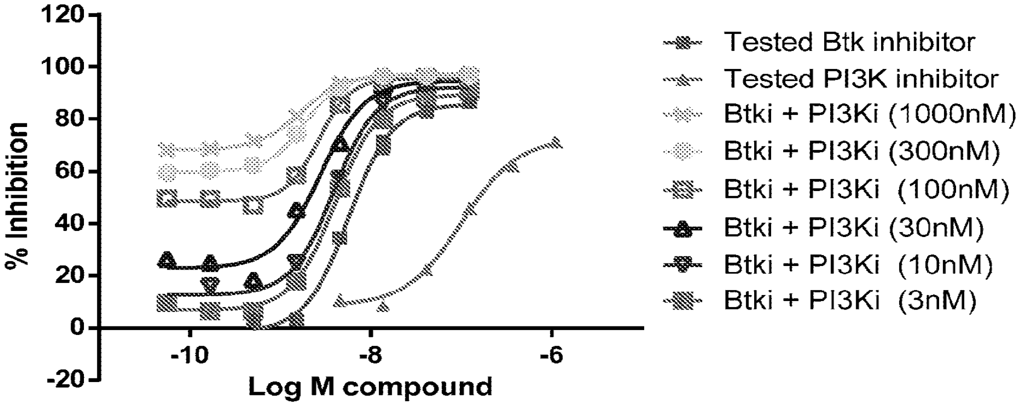

120
100
80
60
40
20
0
-20
% Inhibition
-10
-8
-6
Log M compound
Tested Btk inhibitor
Tested PI3K inhibitor
Btki + PI3Ki (1000nM)
Btki + PI3Ki (300nM)
Btki + PI3Ki (100nM)
Btki + PI3Ki (30nM)
Btki + PI3Ki (10nM)
Btki + PI3Ki (3nM)

FIG. 1

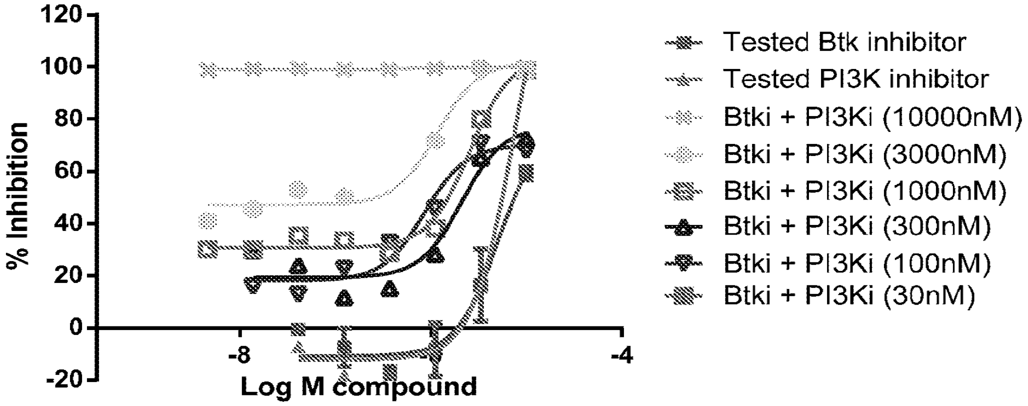

120
100
80
60
40
20
0
-20
% Inhibition
-8
-4
Log M compound
Tested Btk inhibitor
Tested PI3K inhibitor
Btki + PI3Ki (10000nM)
Btki + PI3Ki (3000nM)
Btki + PI3Ki (1000nM)
Btki + PI3Ki (300nM)
Btki + PI3Ki (100nM)
Btki + PI3Ki (30nM)

FIG. 2

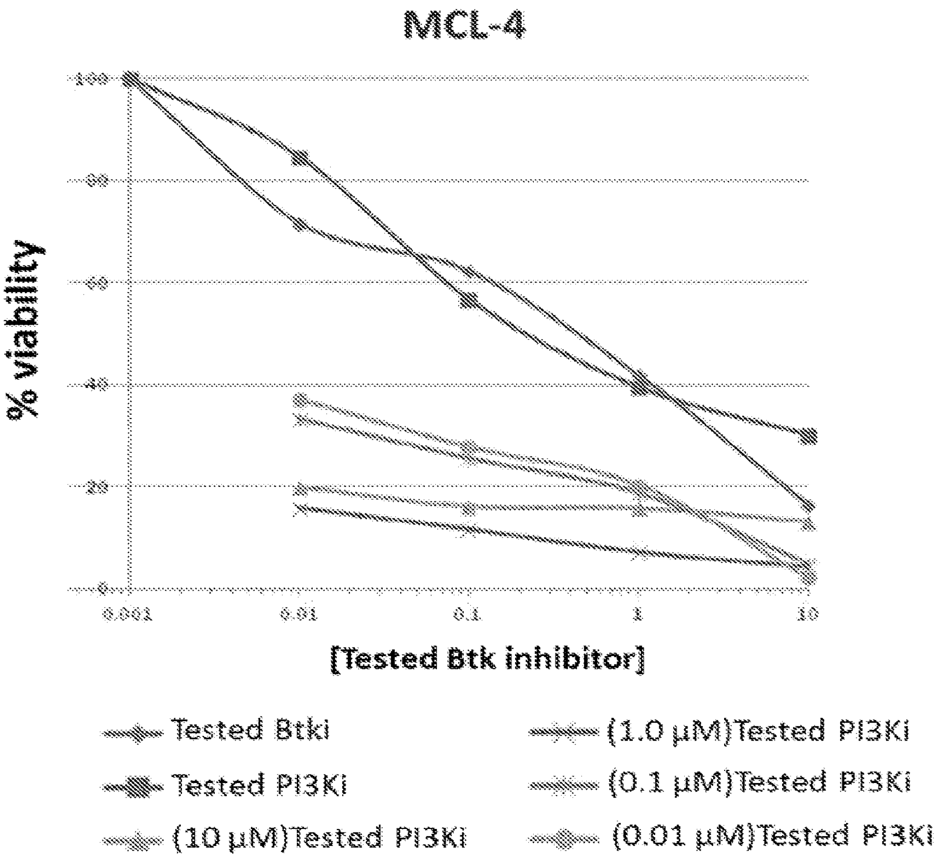

MCL-4
% viability
100
80
60
40
20
0
0.001
0.01
0.1
1
10
[Tested Btk inhibitor]
Tested Btki
Tested PI3Ki
(10 μM)Tested PI3Ki
(1.0 μM)Tested PI3Ki
(0.1 μM)Tested PI3Ki
(0.01 μM)Tested PI3Ki

FIG. 3

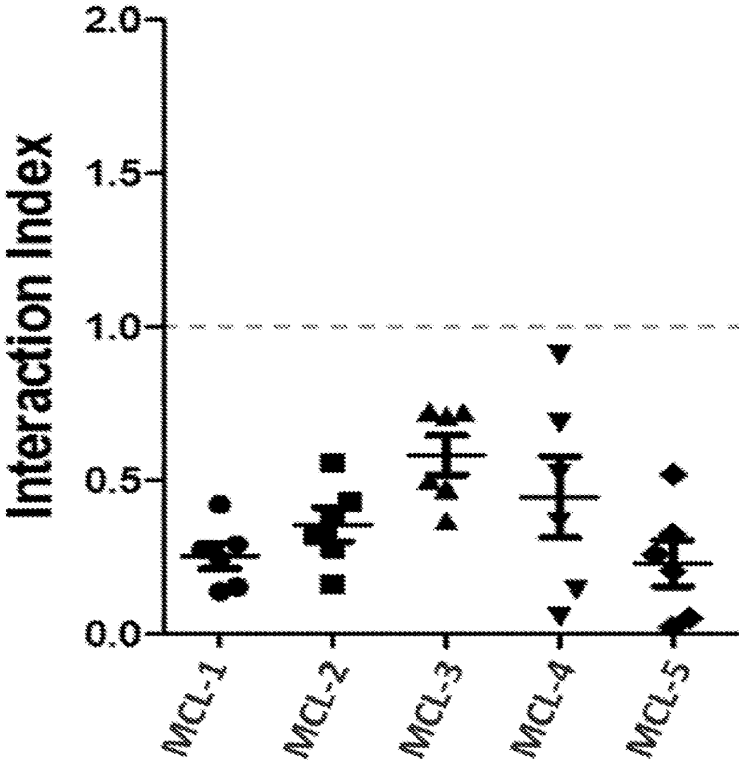


FIG. 4

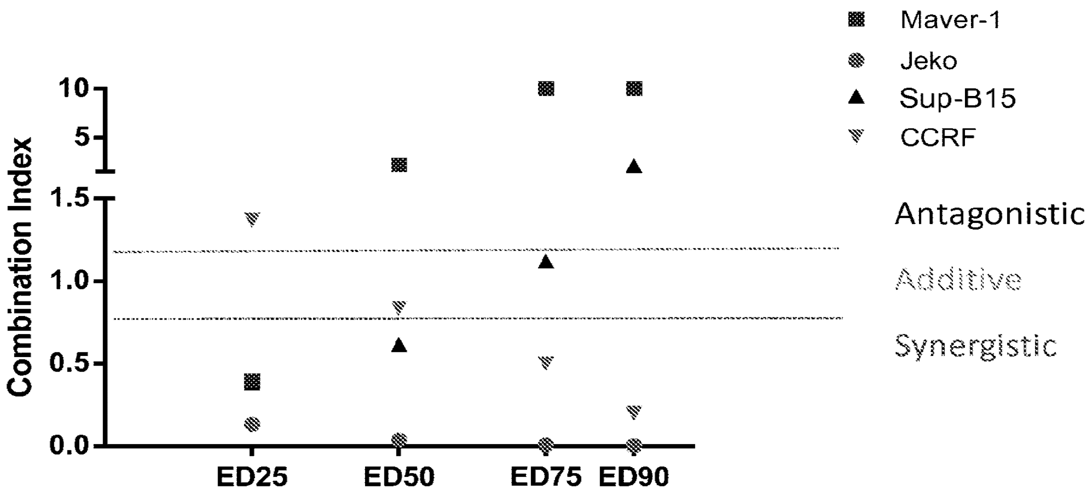

Maver-1
Jeko
Sup-B15
CCRF
Combination Index
10
5
1.5
1.0
0.5
0.0
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 5

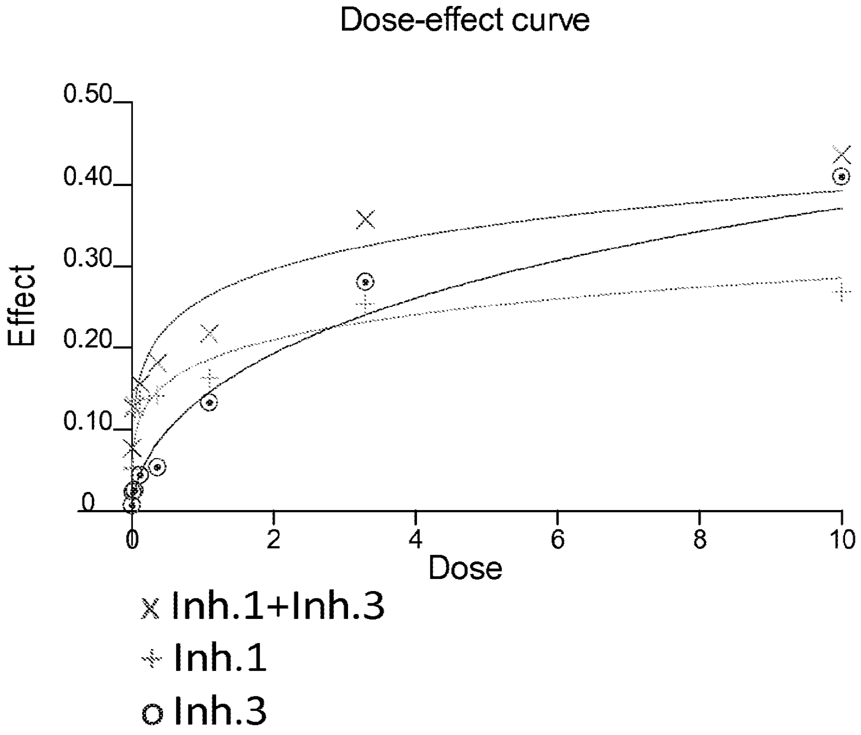

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
Dose
0
2
4
6
8
10
× Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 6

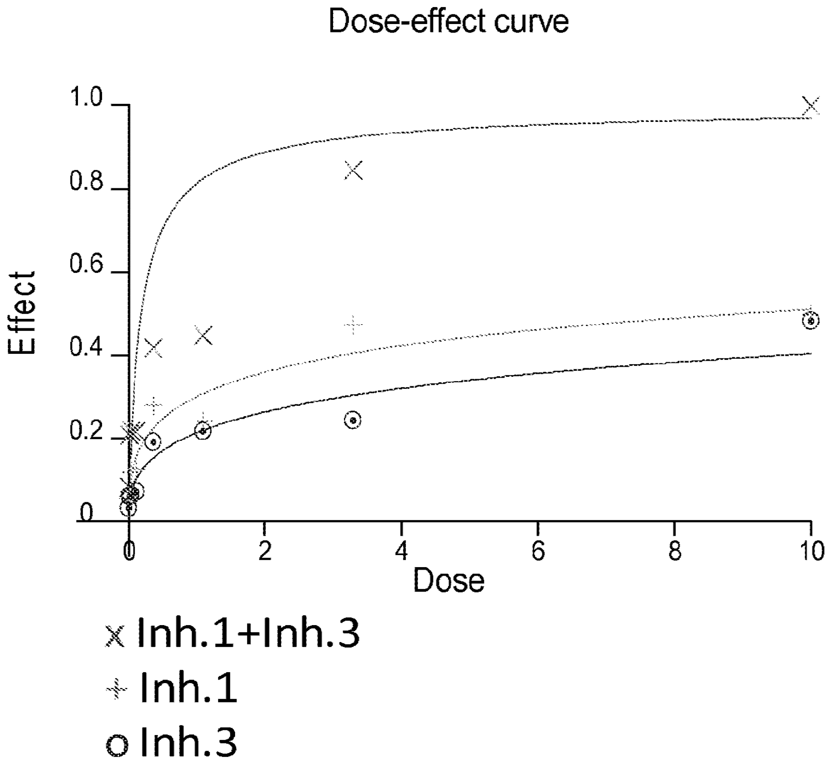

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
Dose
0
2
4
6
8
10
× Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 7

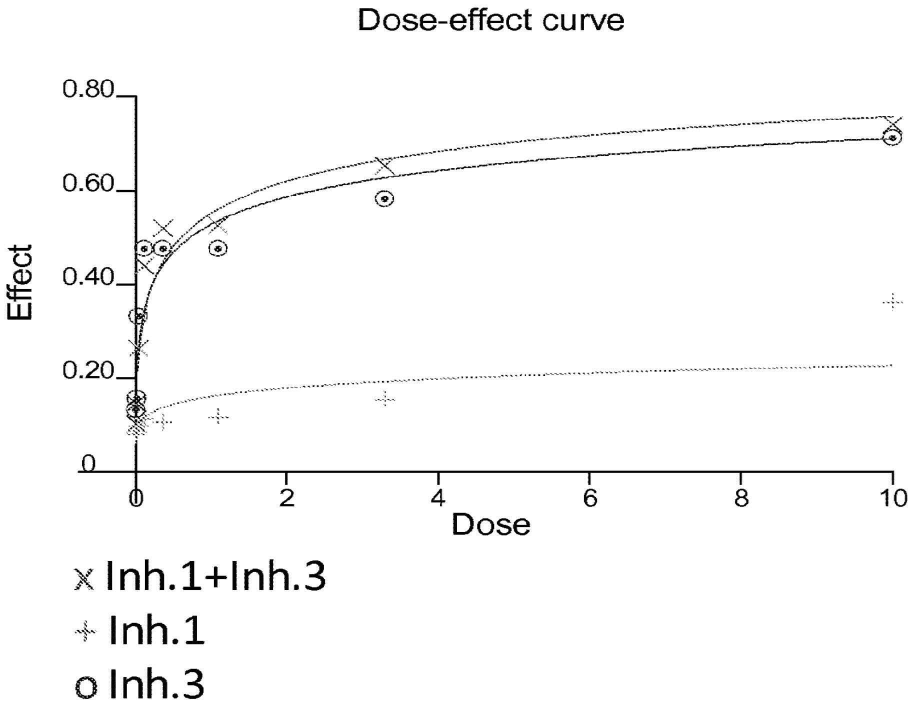

Dose-effect curve
Effect
0.80
0.60
0.40
0.20
0
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 8

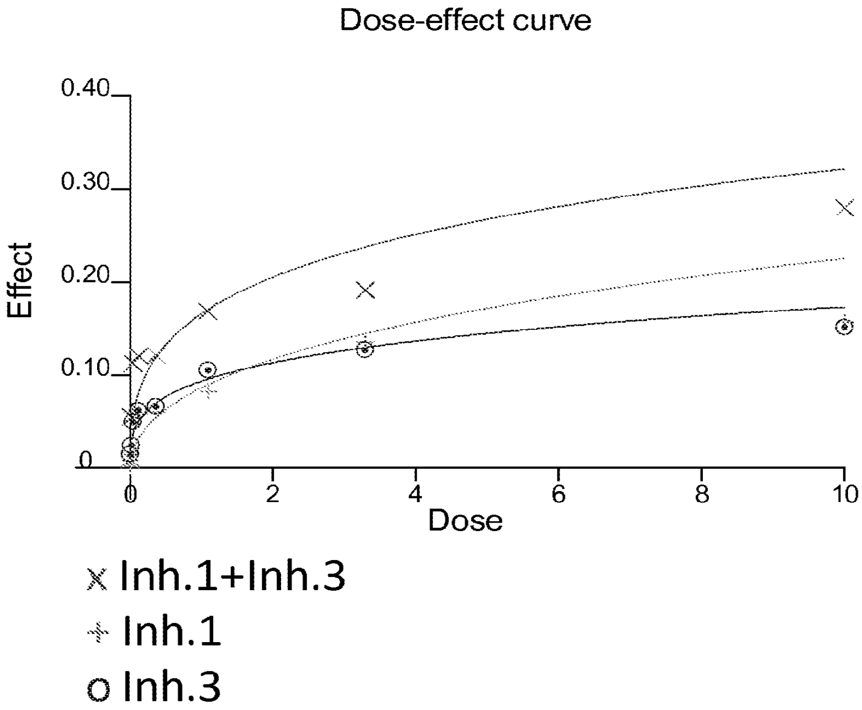

Dose-effect curve
Effect
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 9

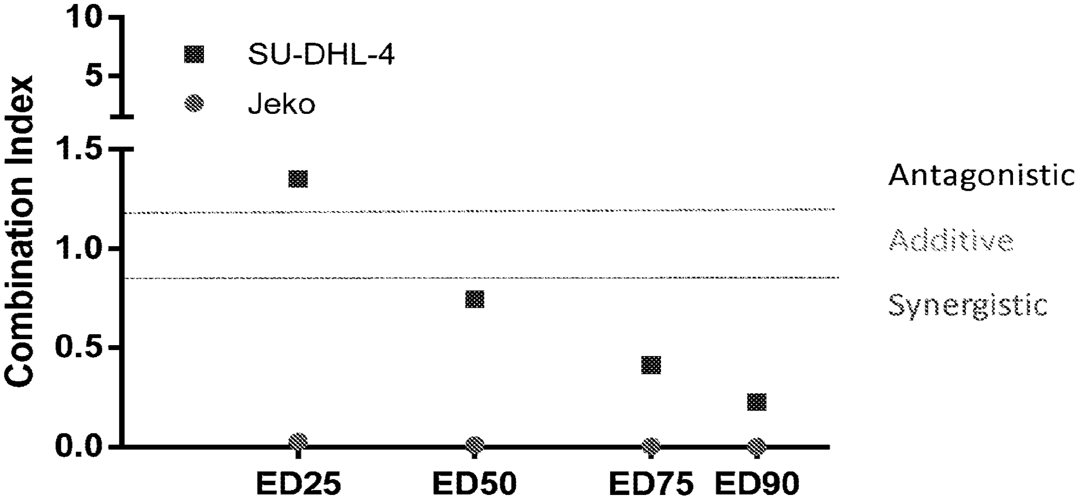

Combination Index
10
5
1.5
1.0
0.5
0.0
SU-DHL-4
Jeko
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 10

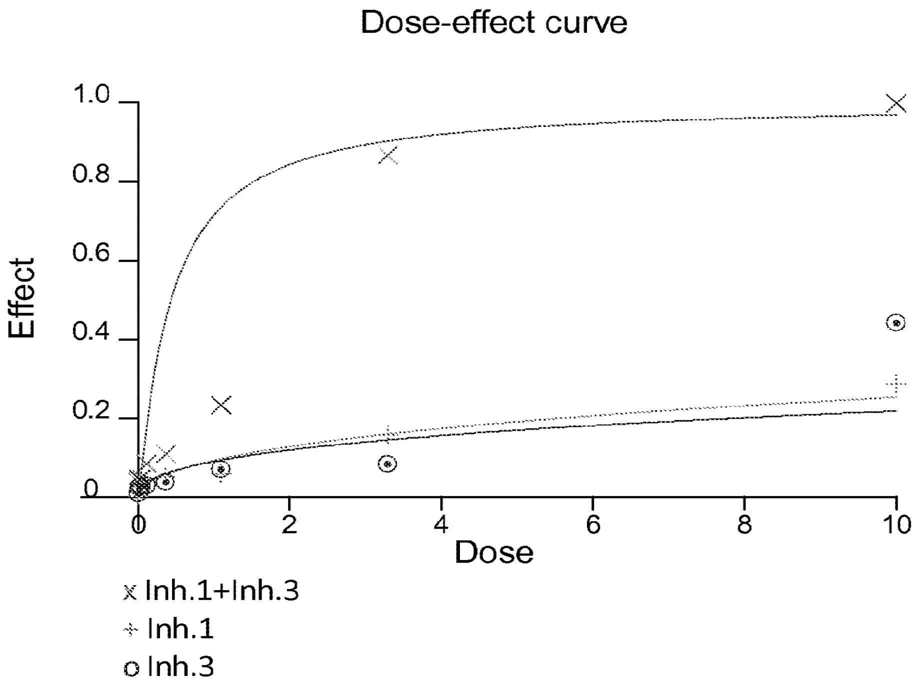

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 11

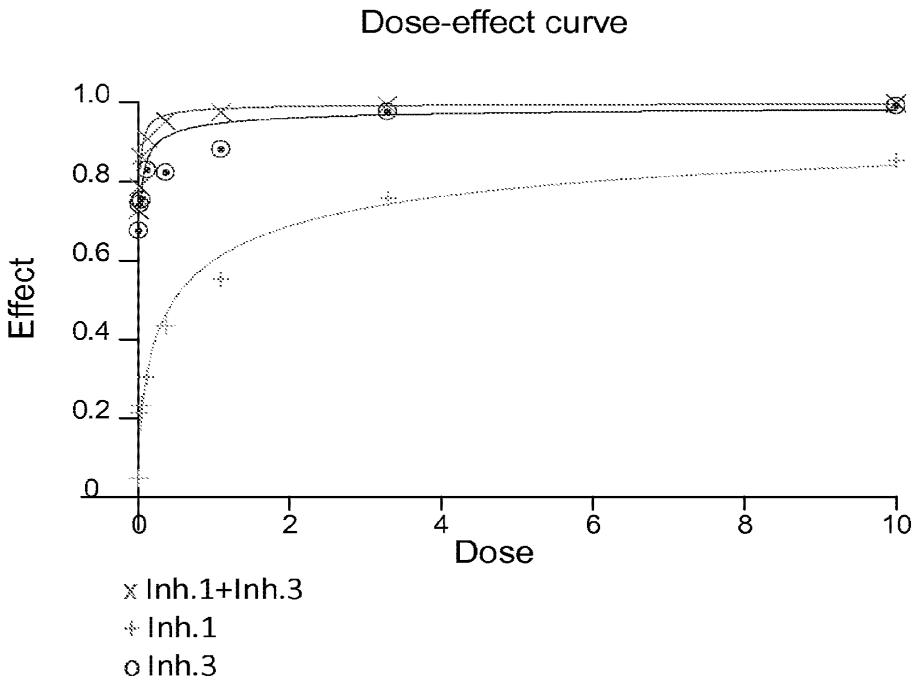

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 12

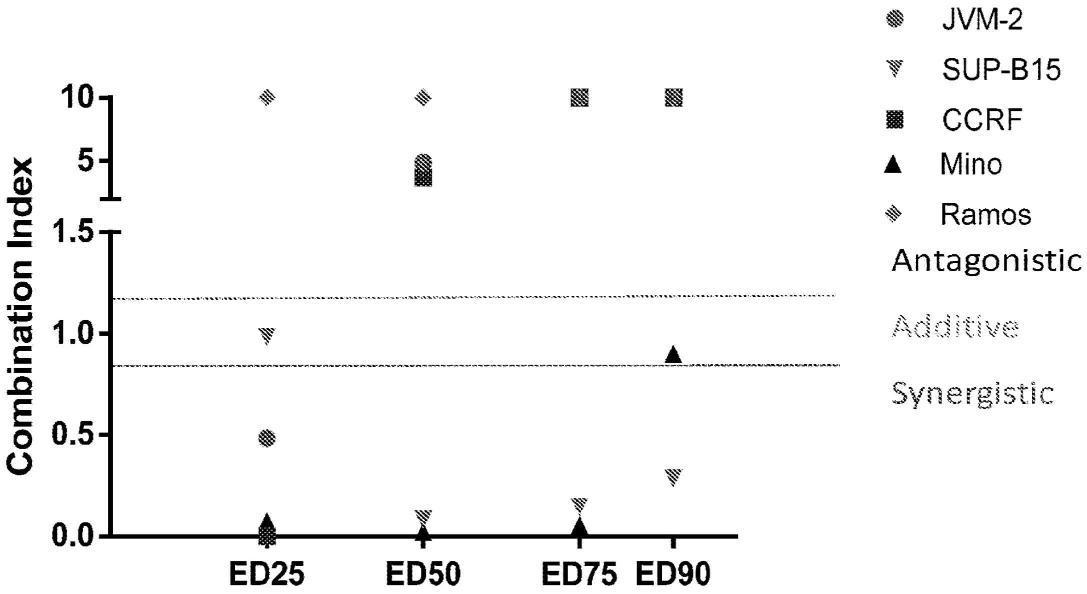

Combination Index
10
5
1.5
1.0
0.5
0.0
ED25
ED50
ED75
ED90
JVM-2
SUP-B15
CCRF
Mino
Ramos
Antagonistic
Additive
Synergistic

FIG. 13

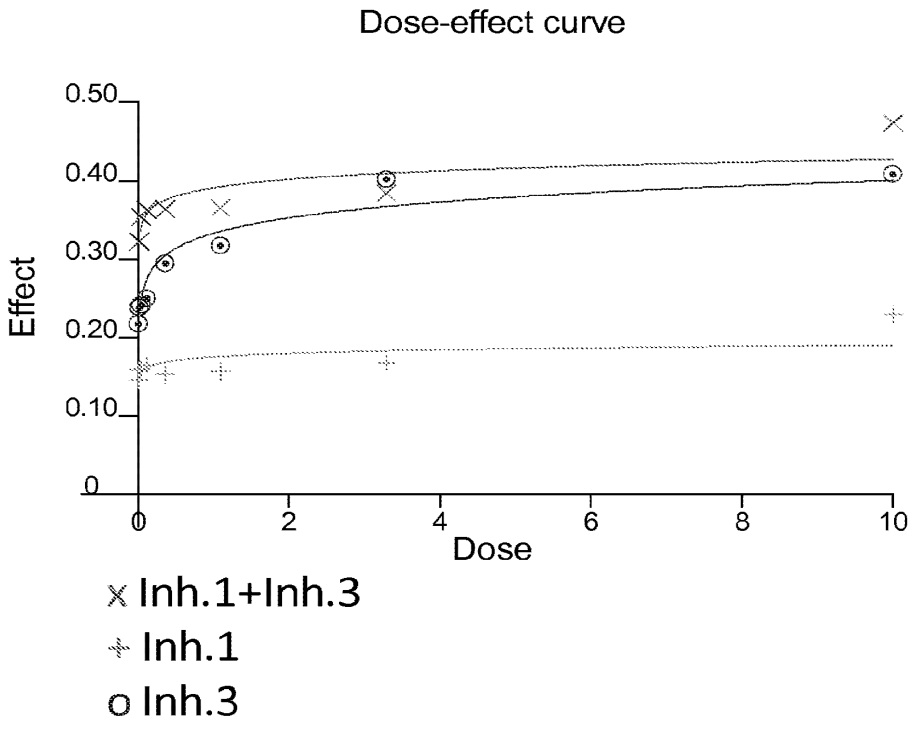

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
× Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 14

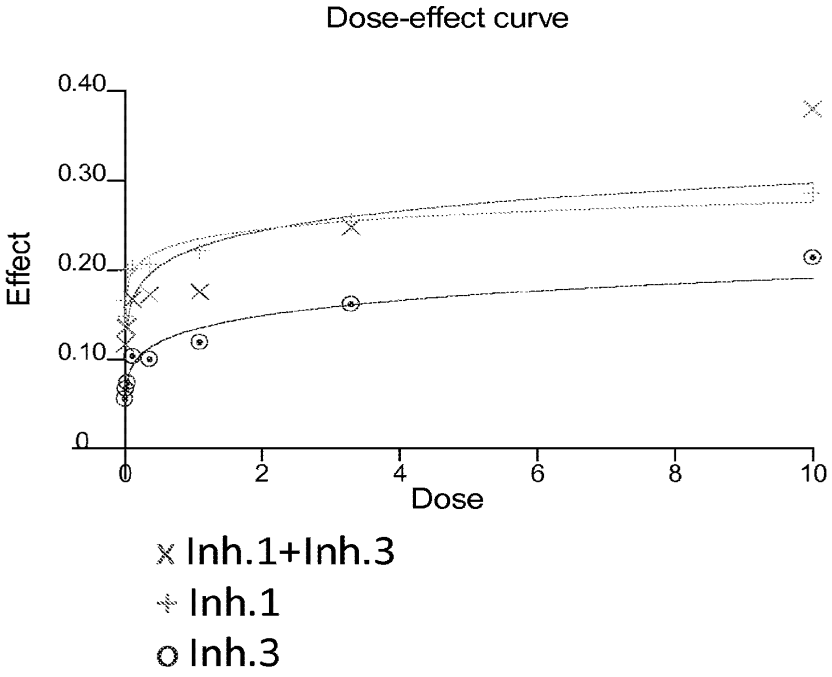
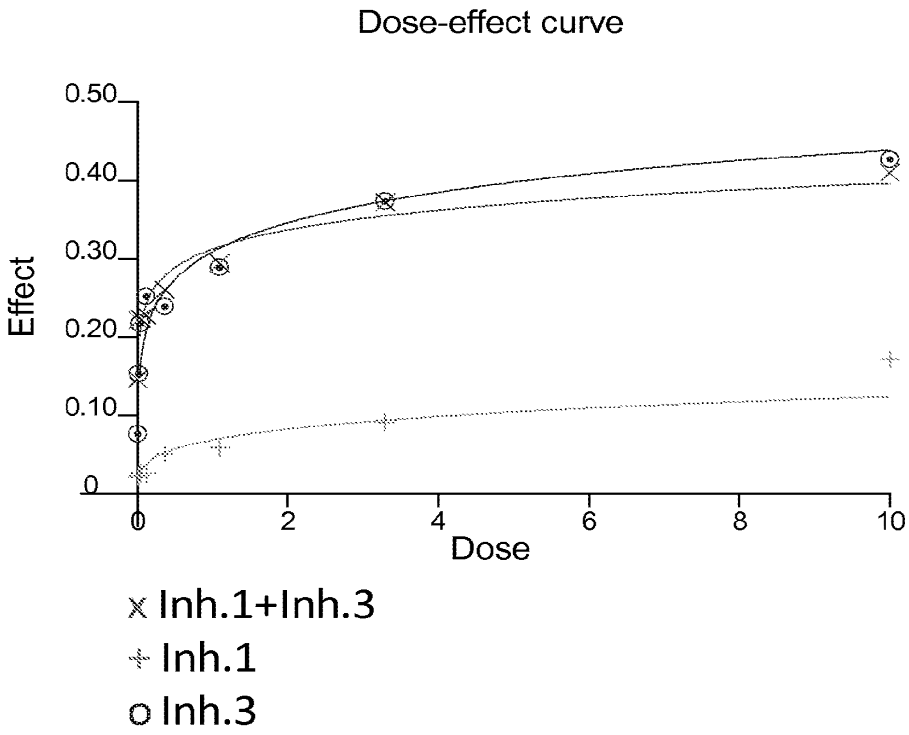

Dose-effect curve
Effect
0.40
0.30
0.20
0.10
0
Dose
0
2
4
6
8
10
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 15



Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
Dose
0
2
4
6
8
10
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 16

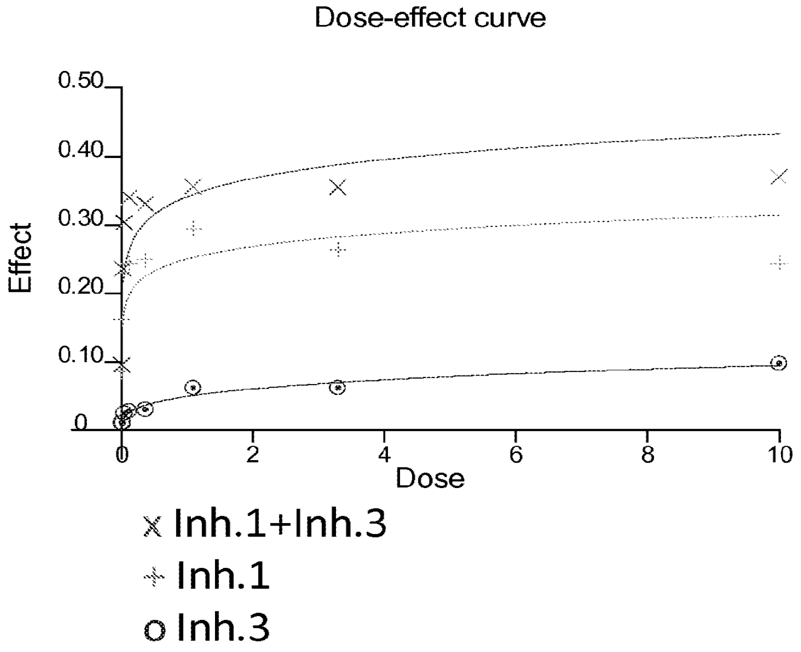

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
Dose
0
2
4
6
8
10
× Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 17

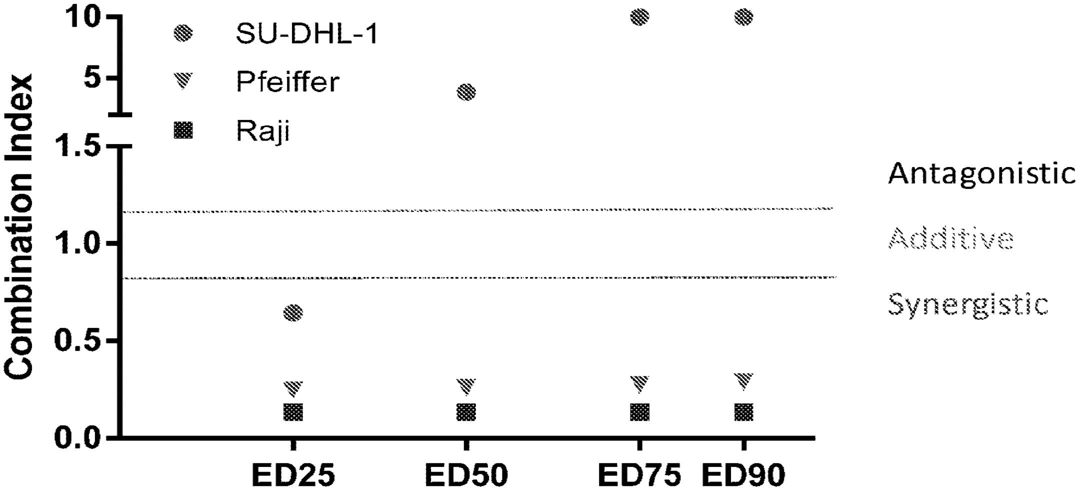

Combination Index
10
5
1.5
1.0
0.5
0.0
SU-DHL-1
Pfeiffer
Raji
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 18

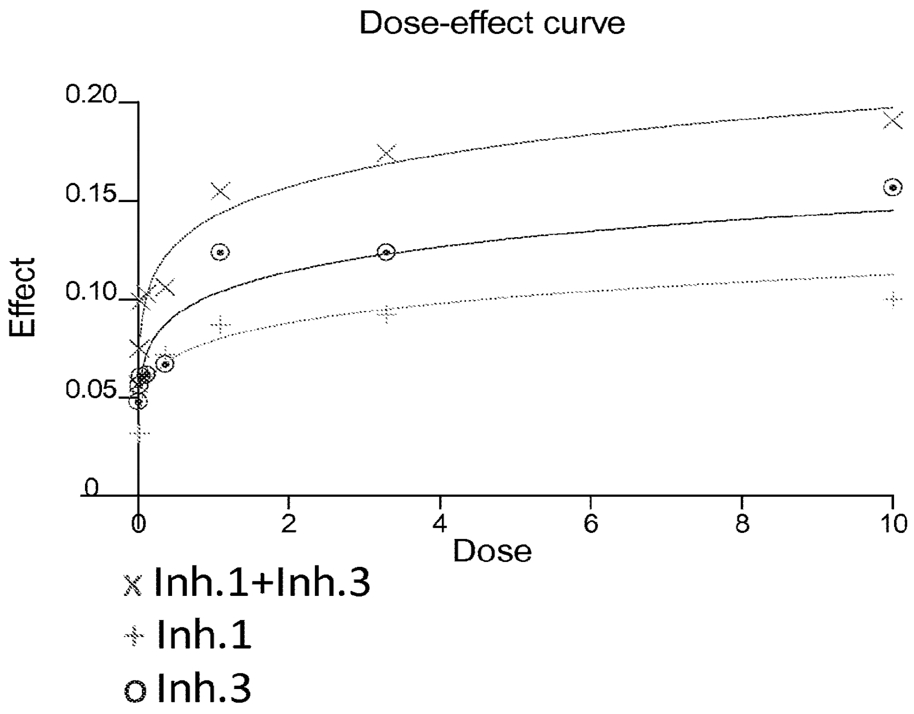

Dose-effect curve
Effect
0.20
0.15
0.10
0.05
0
Dose
0
2
4
6
8
10
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 19

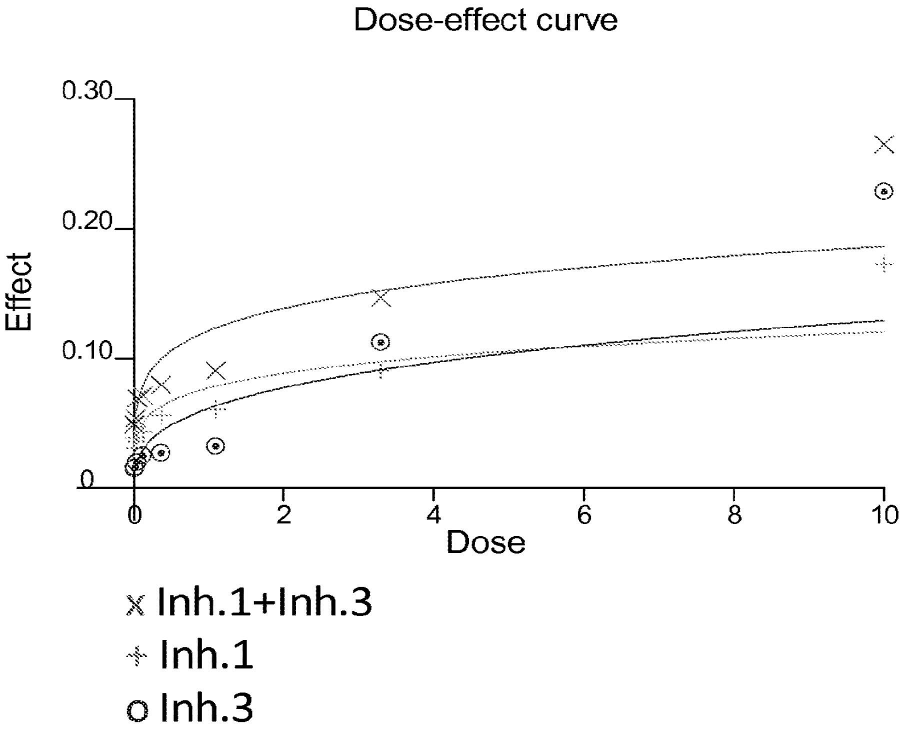

Dose-effect curve
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 20

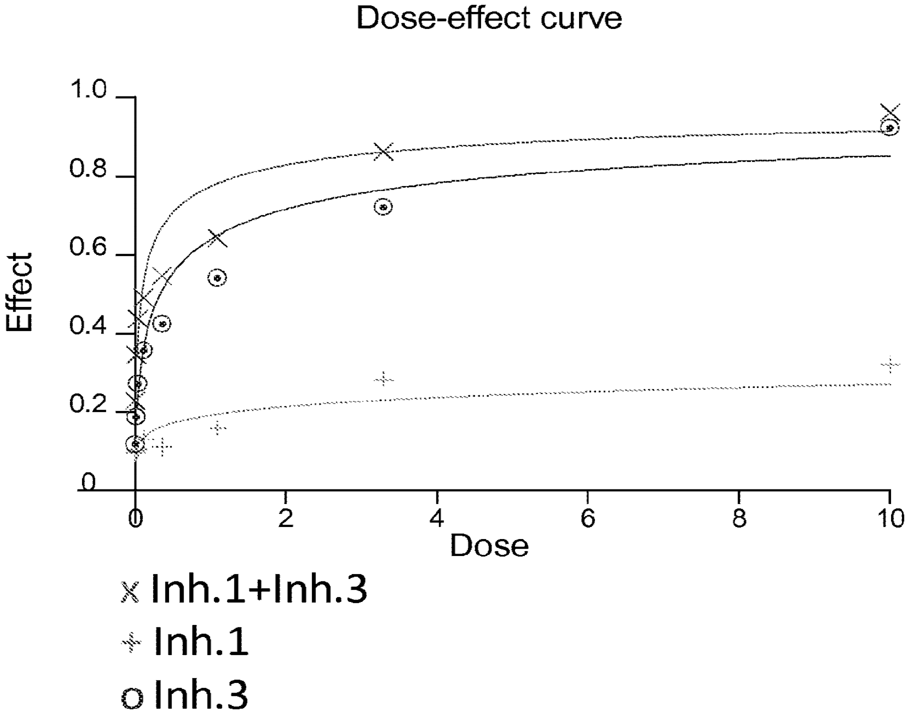

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 21

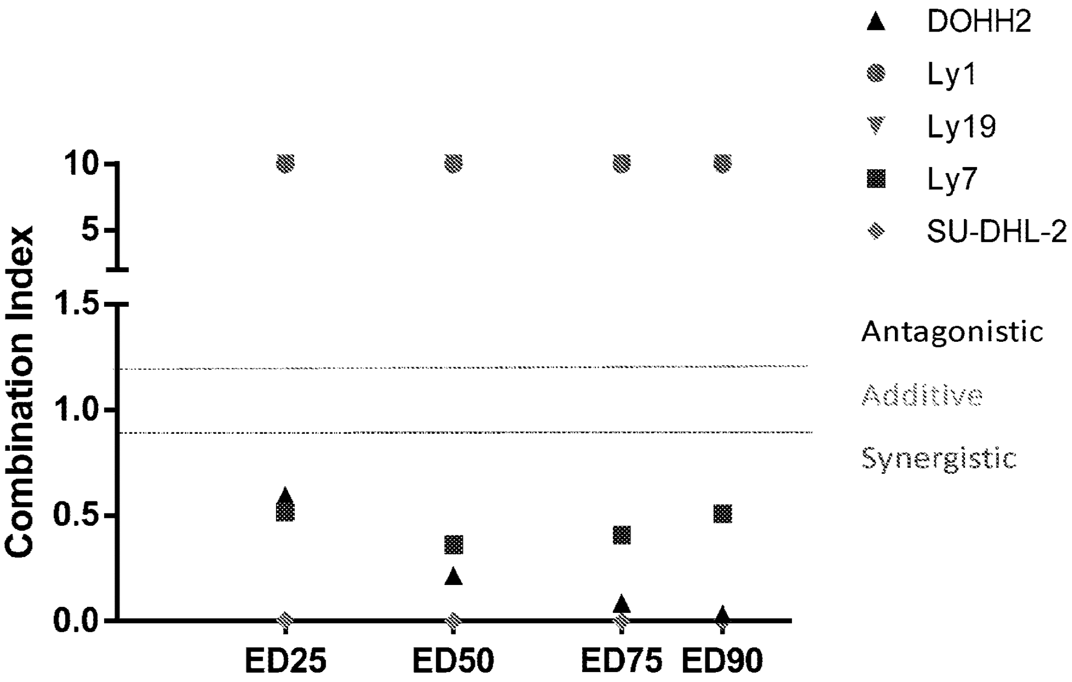

▲ DOHH2
● Ly1
▼ Ly19
■ Ly7
◆ SU-DHL-2
Combination Index
10
5
1.5
1.0
0.5
0.0
ED25
ED50
ED75
ED90
Antagonistic
Additive
Synergistic

FIG. 22

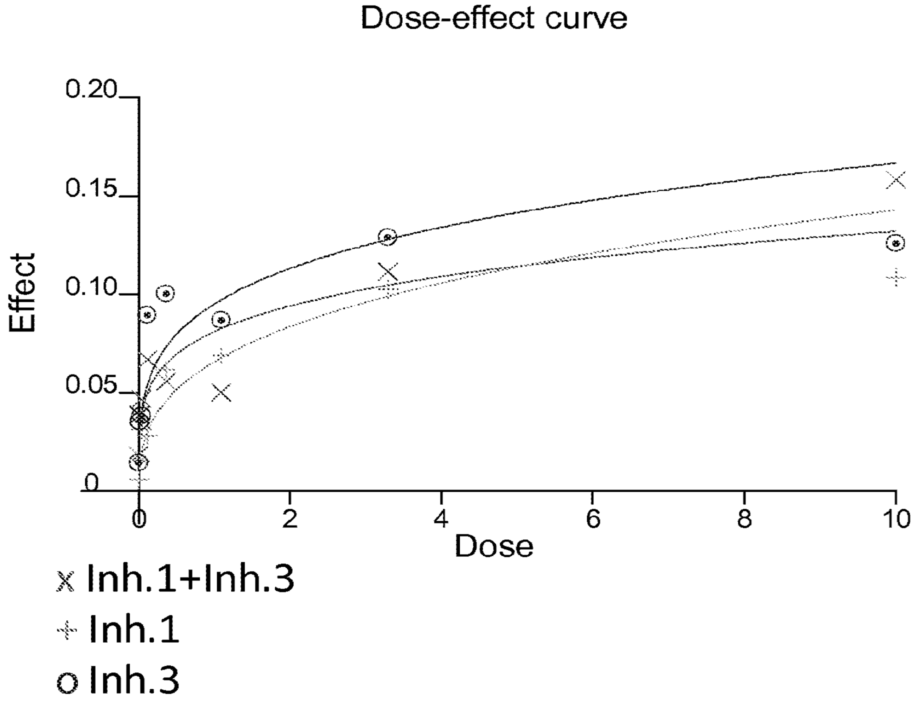

Dose-effect curve
Effect
0.20
0.15
0.10
0.05
0
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 23

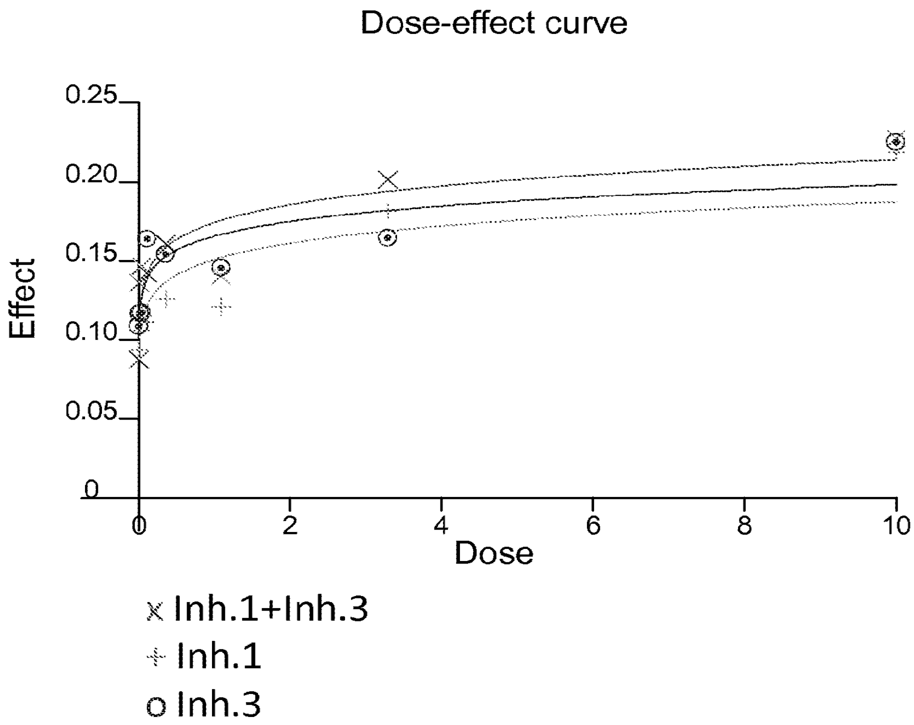

Dose-effect curve
0.25
0.20
0.15
0.10
0.05
0
Effect
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 24

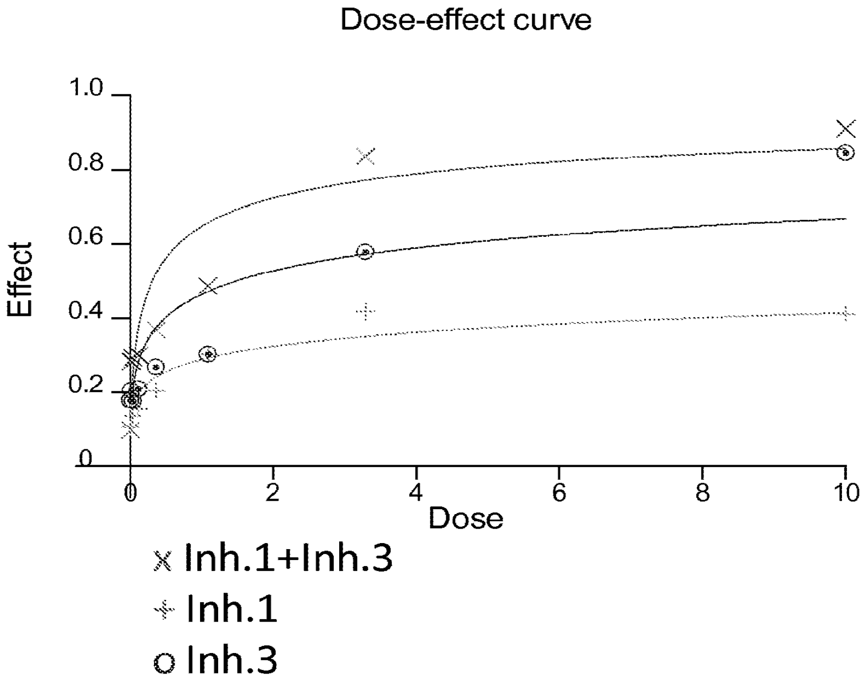

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
Dose
0
2
4
6
8
10
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 25

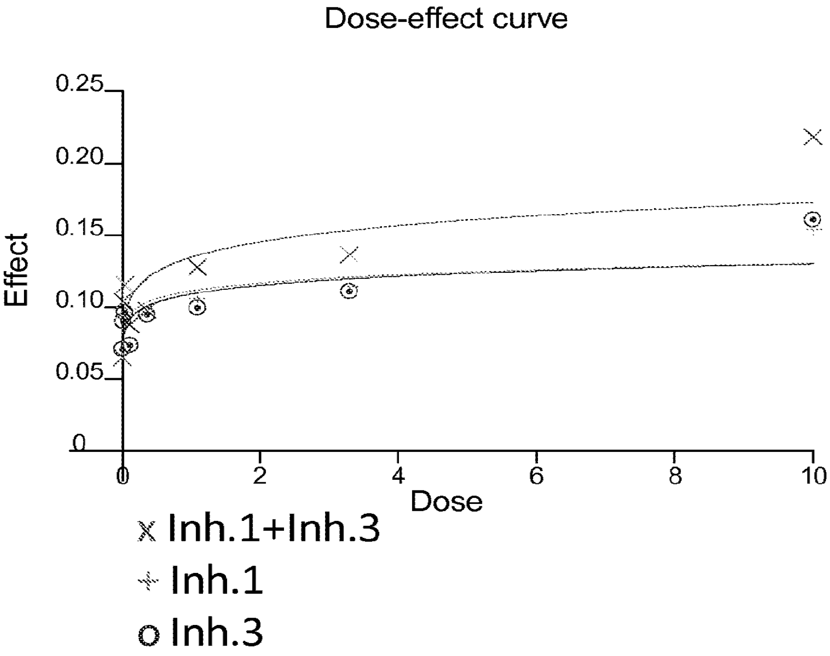

Dose-effect curve
Effect
0.25
0.20
0.15
0.10
0.05
0
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 26

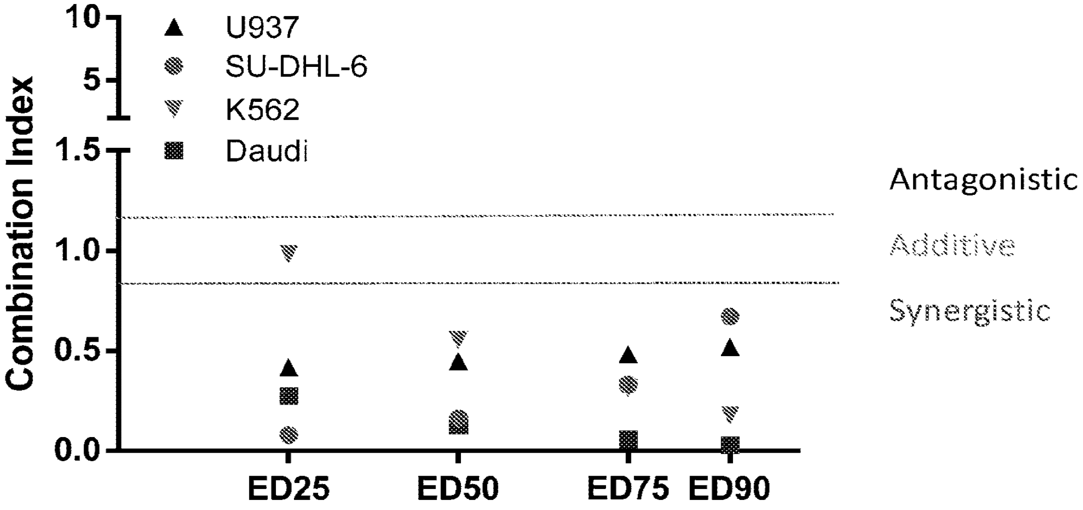

10
5
1.5
1.0
0.5
0.0
Combination Index
U937
SU-DHL-6
K562
Daudi
ED25
ED50
ED75
ED90
Antagonistic
Additive
Synergistic

FIG. 27

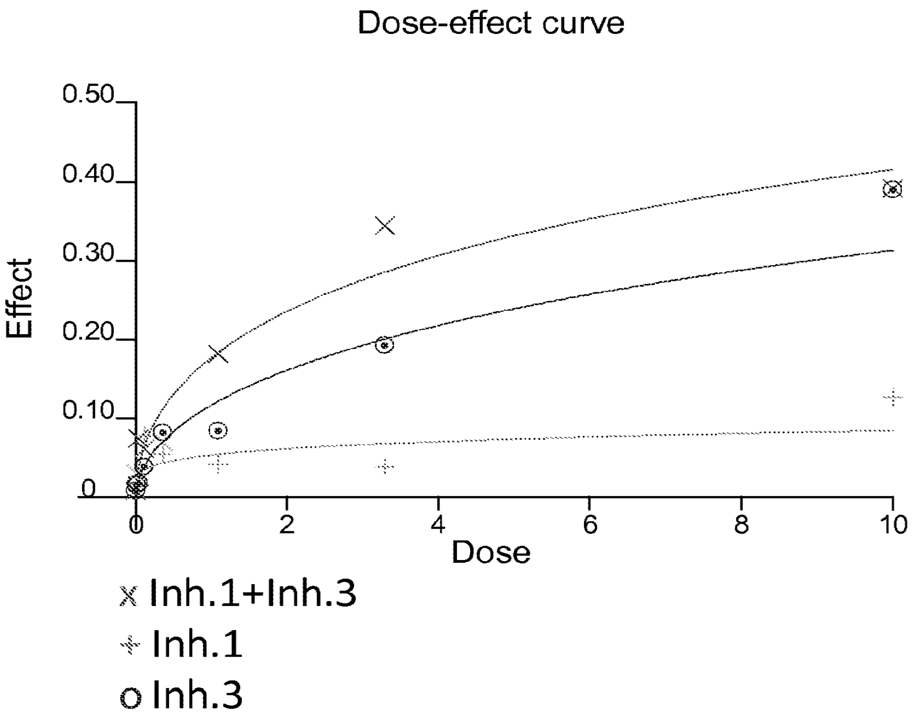

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 28

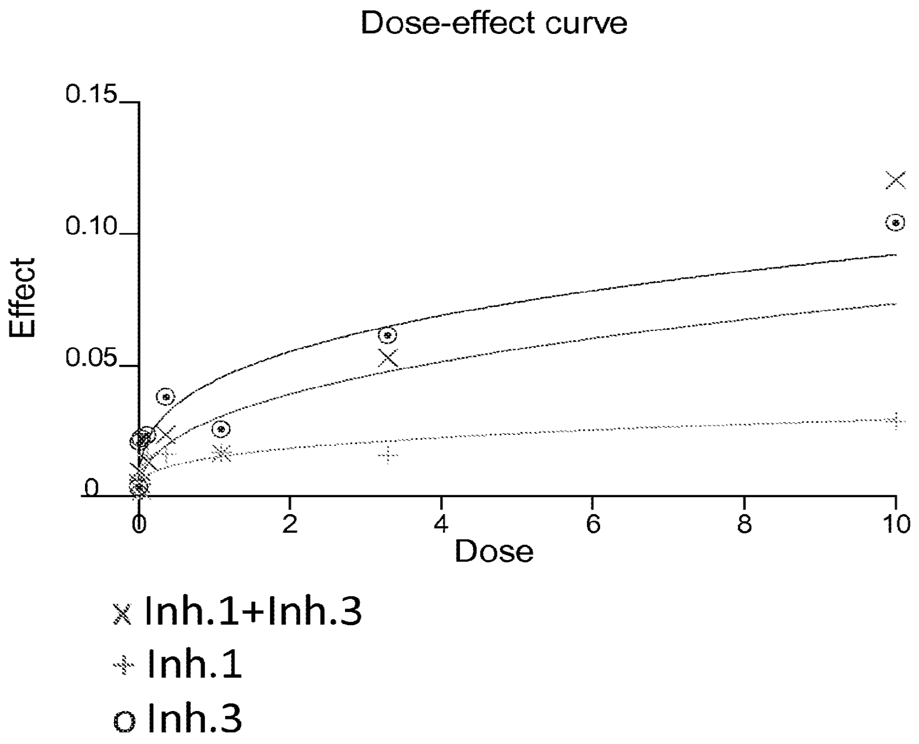

Dose-effect curve
Effect
0.15
0.10
0.05
0
0
2
4
6
8
10
Dose
× Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 29

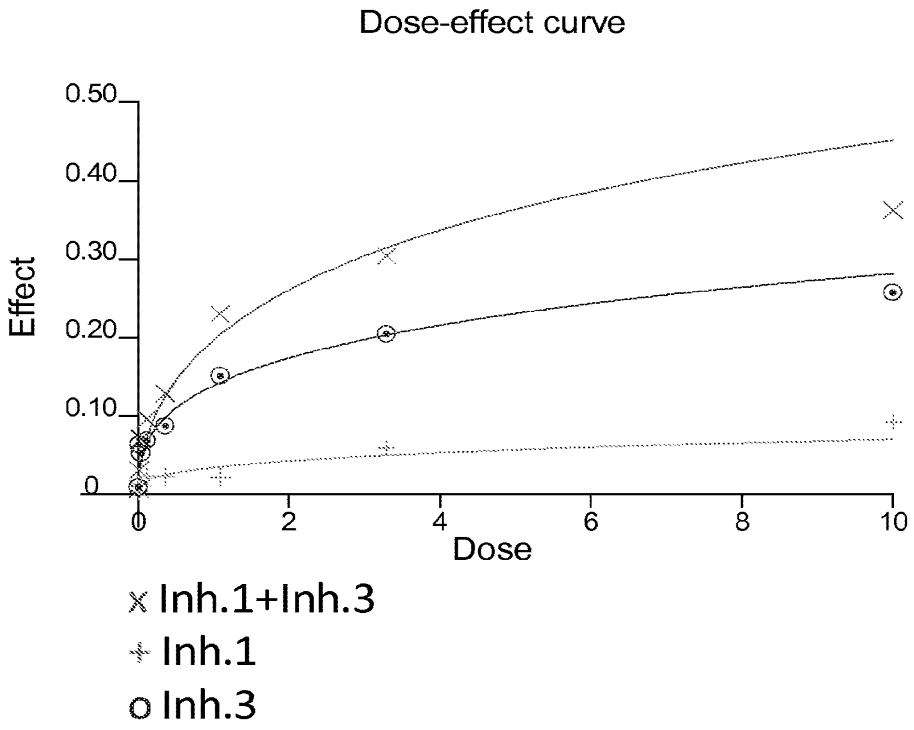
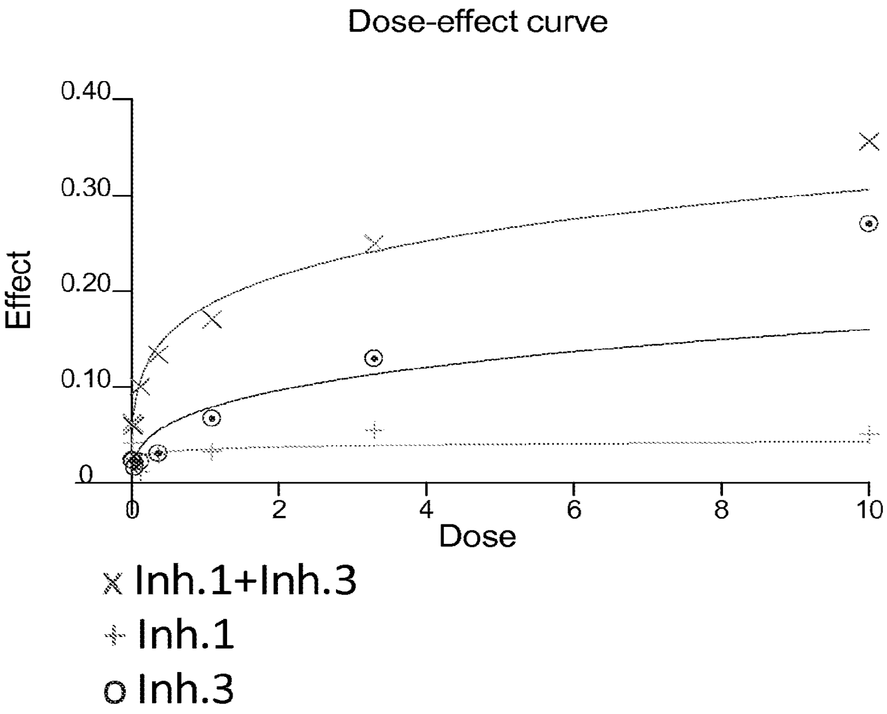

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
Dose
0
2
4
6
8
10
× Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 30



Dose-effect curve
Effect
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 31

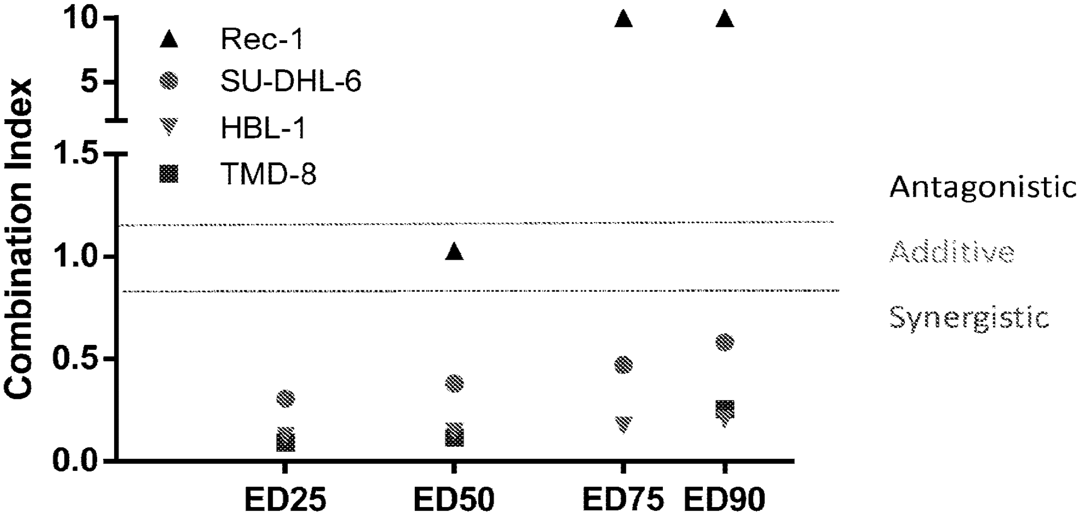

Combination Index
10
5
1.5
1.0
0.5
0.0
▲ Rec-1
● SU-DHL-6
▼ HBL-1
■ TMD-8
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 32

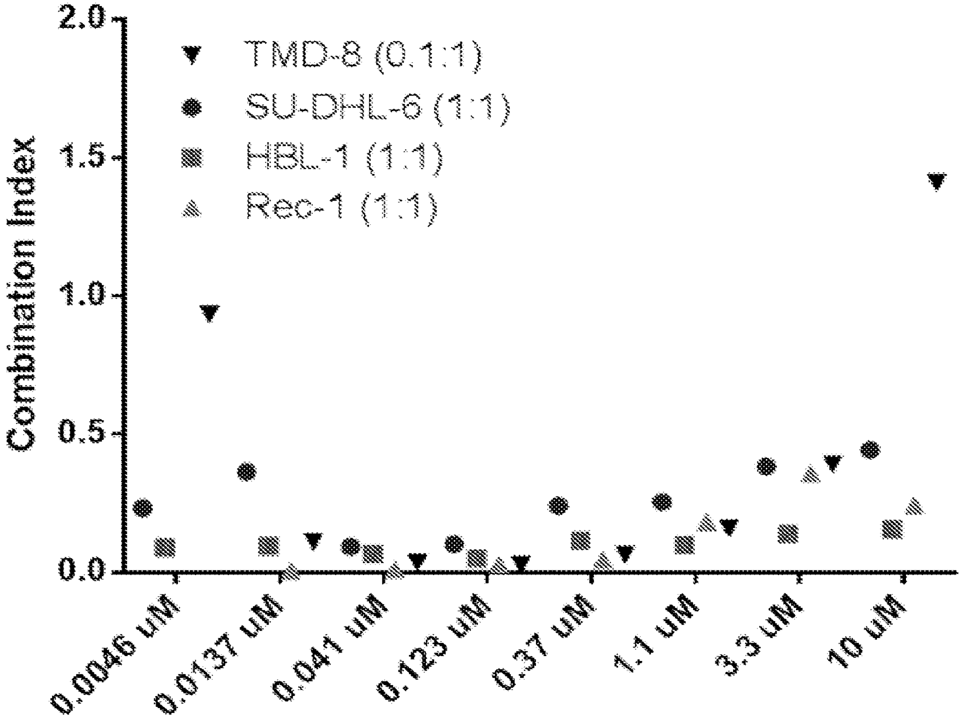

2.0
1.5
1.0
0.5
0.0
Combination Index
▼ TMD-8 (0.1:1)
● SU-DHL-6 (1:1)
■ HBL-1 (1:1)
▲ Rec-1 (1:1)
0.0046 uM
0.0137 uM
0.041 uM
0.123 uM
0.37 uM
1.1 uM
3.3 uM
10 uM

FIG. 33

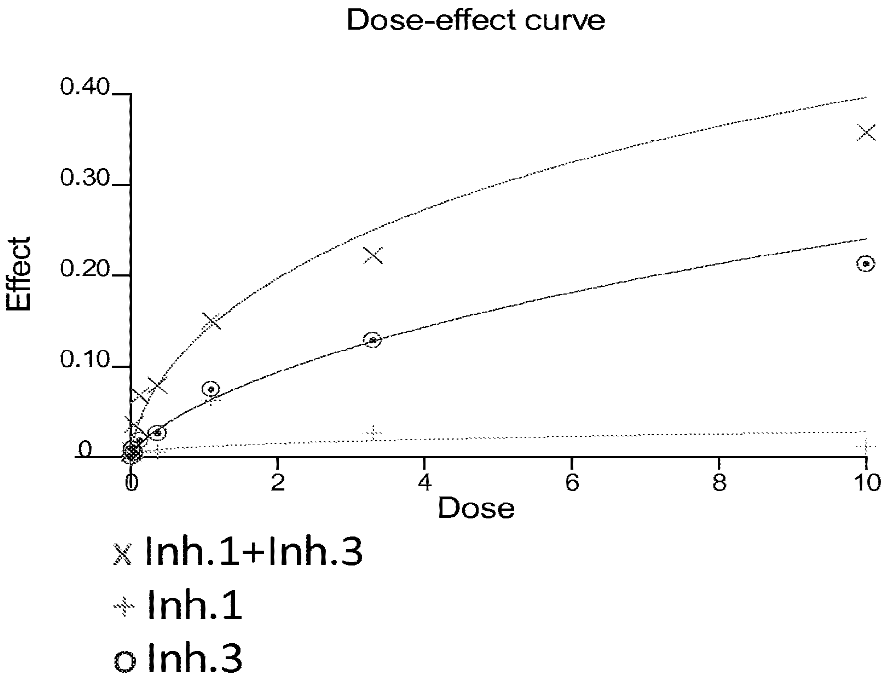

Dose-effect curve
Effect
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
× Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 34

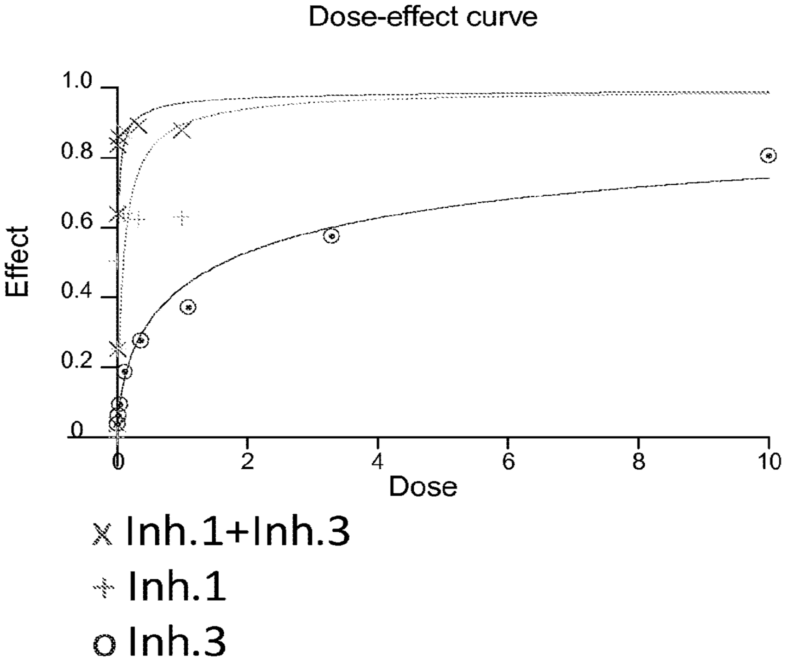

Dose-effect curve
1.0
0.8
0.6
0.4
0.2
0
Effect
0
2
4
6
8
10
Dose
x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 35

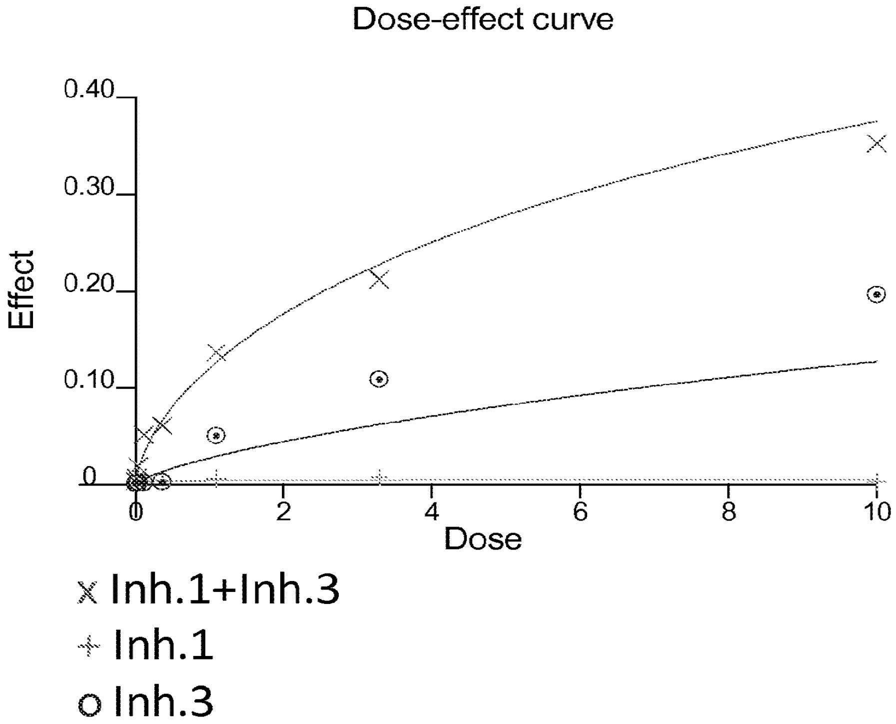

Dose-effect curve
0.40
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 36

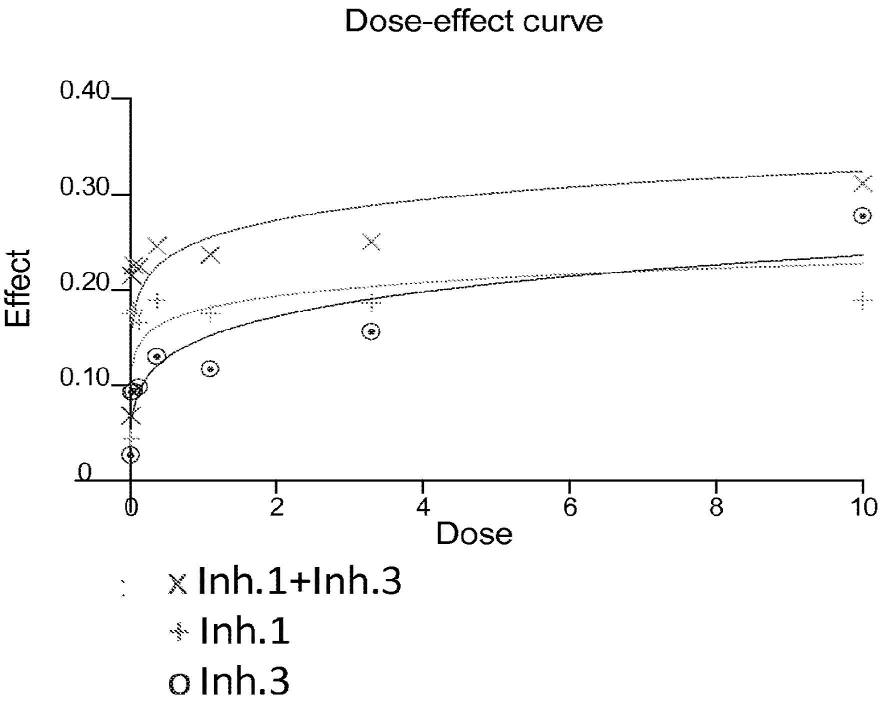

Dose-effect curve
0.40
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 37

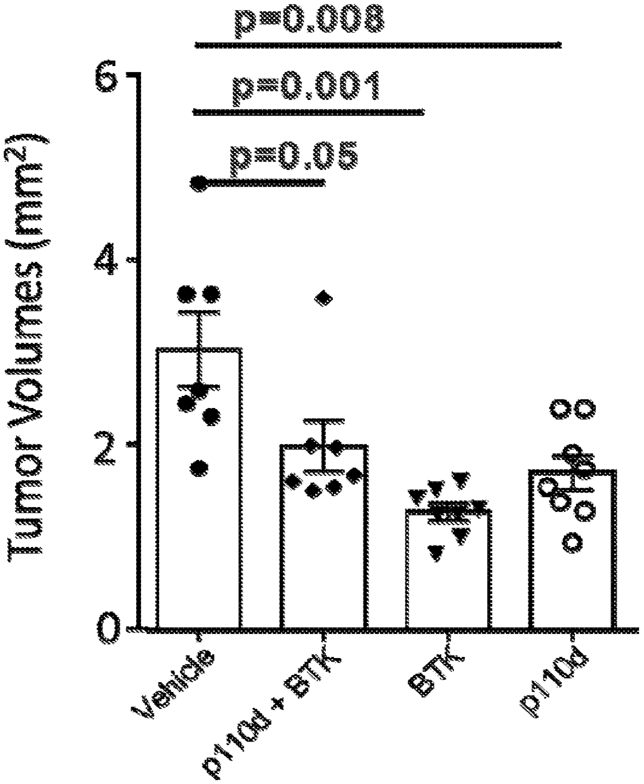

p=0.008
p=0.001
p=0.05
Tumor Volumes (mm^2)
6
4
2
0
Vehicle
p110d + BTK
BTK
p110d

FIG. 38

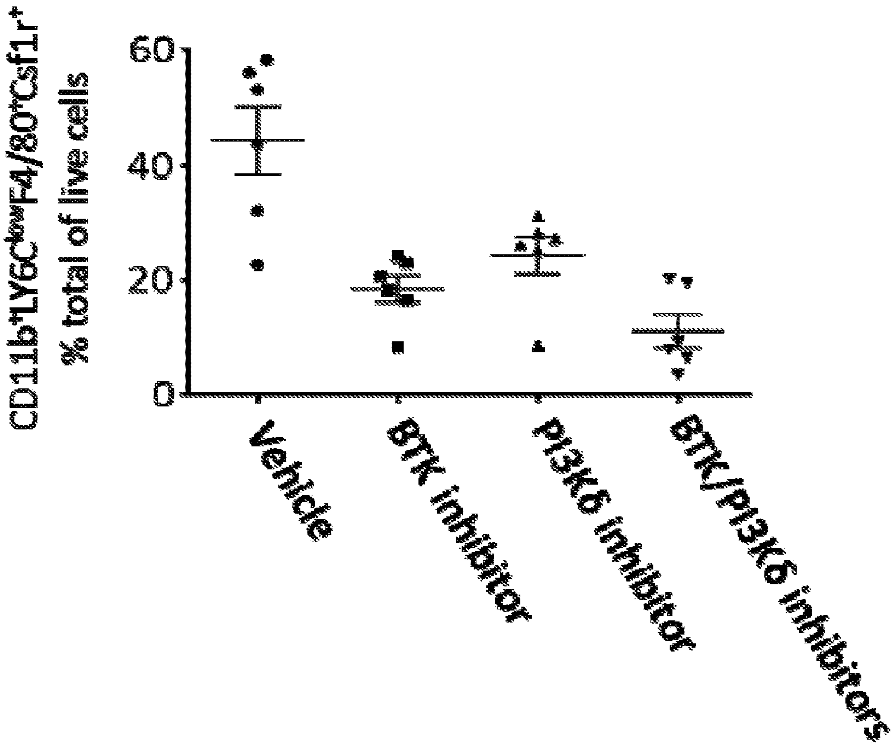

CD11b+LY6ClowF4/80+Csf1r+
% total of live cells
60
40
20
0
Vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 39

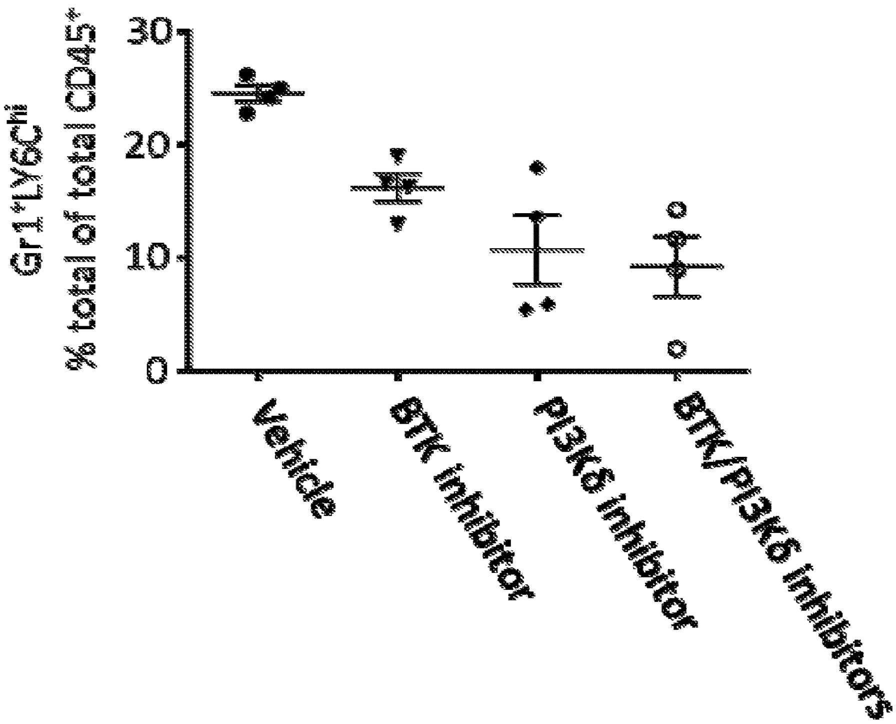

Gr1+LY6Chi
% total of total CD45+
30
20
10
0
Vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 40

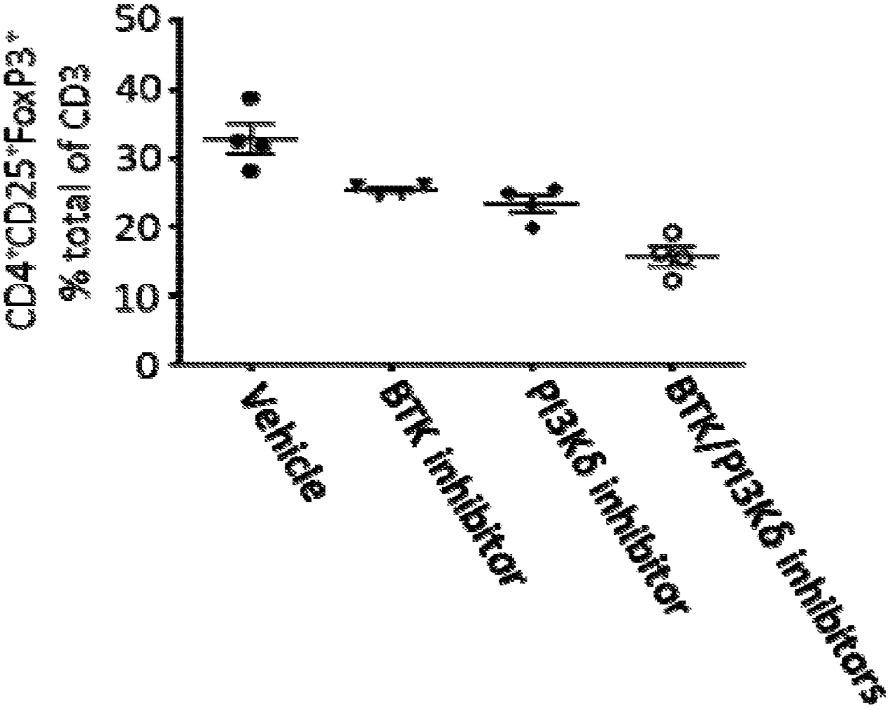

CD4+CD25+FoxP3+
% total of CD3
50
40
30
20
10
0
Vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 41

THERAPEUTIC COMBINATION OF A PI3K INHIBITOR AND A BTK INHIBITOR

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

[002] PI3K inhibitors are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. PI3K inhibitors are key signaling enzymes that relay signals from cell surface receptors to downstream effectors. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3K inhibitors (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases.

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

[004] The delta (δ) isoform of class I PI3K (PI3K-δ) is involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its role in immune system function, PI3K-δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. The gamma (γ) isoform of class I PI3K (PI3K-γ) is also involved in immune system functions and plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

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

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

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

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

[009] In many solid tumors, the supportive microenvironment (which may make up the majority of the tumor mass) is a dynamic force that enables tumor survival. The tumor microenvironment is generally defined as a complex mixture of "cells, soluble factors, signaling molecules, extracellular matrices, and mechanical cues that promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, forster therapeutic resistance, and provide niches for dominant metastases to thrive," as described in Swartz et al., *Cancer Res.*, **2012,** *72,* 2473. Although tumors express antigens that should be recognized by T cells, tumor clearance by the immune system is rare because of immune suppression by the microenvironment. Addressing the tumor cells themselves with e.g. chemotherapy has also proven to be insufficient to overcome the protective effects of the microenvironment. New approaches are thus urgently needed for more effective treatment of solid tumors that take into account the role of the microenvironment.

[0010] The present invention includes the unexpected discovery that the combination of a PI3K inhibitor with a BTK inhibitor is effective in the treatment of any of several types of cancers such as leukemia, lymphoma and solid tumor cancers.

SUMMARY OF THE INVENTION

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

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

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

[0014] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor and a BTK inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[0016] FIG. 1 illustrates the sensitivity of the TMD8 diffuse large B cell lymphoma (DLBCL) cell line to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[0017] FIG. 2 illustrates the sensitivity of the MINO mantle cell lymphoma cell to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[0018] FIG. 3 illustrates the proprofliferative activity in primary mantle cell lymphoma cells of Formula XVIII ("Tested Btki") and Formula IX ("Tested PI3Ki"). The percentage viability of cells ("% viability", y-axis) is plotted versus the concentration of the Formula XVIII ("[Tested Btk Inhibitor]", x-axis). The concentration of the individual BTK and PI3K inhibitors (i.e. not in combination) are also given on the x-axis.

[0019] FIG. 4 illustrates the interaction index of the combination of the BTK inhibitor of Formula XVIII and the PI3K inhibitor of Formula IX in primary mantle cell lymphoma cells.

[0020] FIG. 5 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include Maver-1 (B cell lymphoma, mantle), Jeko (B cell lymphoma, mantle), CCRF (B lymphoblast, acute lymphoblastic leukemia), and SUP-B15 (B lymphoblast, acute lymphoblastic leukemia). The dose-effect curves for these cell lines are given in FIG. 6, FIG. 7, FIG. 8, and FIG. 9. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation).

[0021] FIG. 6 illustrates the dose-effect curves obtained for the tested Maver-1 cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0022] FIG. 7 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0023] FIG. 8 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0024] FIG. 9 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0025] FIG. 10 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include Jeko (B cell lymphoma, mantle cell lymphoma) and SU-DHL-4 (activated B cell like (ABC) diffuse large B cell lymphoma). The dose-effect curves for these cell lines are given in FIG. 11 and FIG. 12.

[0026] FIG. 11 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0027] FIG. 12 illustrates the dose-effect curves obtained for the tested SU-DHL-4 cell line (diffuse large B cell lymphoma, ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0028] FIG. 13 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include CCRF (B lymphoblast, acute lymphoblastic leukemia), SUP-B15 (B lymphoblast, acute lymphoblastic leukemia), JVM-2 (prolymphocytic leukemia), Ramos (Burkitt's lymphoma), and Mino (mantle cell lymphoma). The dose-effect curves for these cell lines are given in FIG. 14, FIG. 15, FIG. 16, and FIG. 17. No dose-effect curve is given for Ramos (Burkitt's lymphoma) because of negative slope.

[0029] FIG. 14 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0030] FIG. 15 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0031] FIG. 16 illustrates the dose-effect curves obtained for the tested JVM-2 cell line (prolymphocytic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0032] FIG. 17 illustrates the dose-effect curves obtained for the tested Mino cell line (mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0033] FIG. 18 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include Raji (B lymphocyte, Burkitt's lymphoma), SU-DHL-1 (DLBCL-ABC), and Pfeiffer (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 19, FIG. 20, and FIG. 21.

[0034] FIG. 19 illustrates the dose-effect curves obtained for the tested Raji cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0035] FIG. 20 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0036] FIG. 21 illustrates the dose-effect curves obtained for the tested Pfeiffer cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0037] FIG. 22 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include Ly1 (Germinal center B-cell like diffuse large B-cell lymphoma, DLBCL-GCB), Ly7 (DLBCL-GCB), Ly19 (DLBCL-GCB), SU-DHL-2 (Activated B-cell like diffuse large B-cell lymphoma, DLBCL-ABC), and DOHH2 (follicular lymophoma, FL). The dose-effect curves for these cell lines are given in FIG. 23, FIG. 24, FIG. 25, and FIG. 26, except for the Ly19 cell line, which is not graphed because of a negative slope.

[0038] FIG. 23 illustrates the dose-effect curves obtained for the tested Ly1 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0039] FIG. 24 illustrates the dose-effect curves obtained for the tested Ly7 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0040] FIG. 25 illustrates the dose-effect curves obtained for the tested DOHH2 cell line (FL) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0041] FIG. 26 illustrates the dose-effect curves obtained for the tested SU-DHL-2 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0042] FIG. 27 illustrates the synergy observed in certain cell lines when Formula (XVIII) and Formula (IX) are combined. The tested cell lines include U937 (histiocytic lymphoma and/or myeloid), K562 (leukemia, myeloid, and/or chronic myelogenous leukemia), Daudi (human Burkitt's lymphoma), and SU-DHL-6 (DLBCL-GCB and/or peripheral T-cell lymphoma, PTCL). The dose-effect curves for these cell lines are given in FIG. 28, FIG. 29, FIG. 30, and FIG. 31.

[0043] FIG. 28 illustrates the dose-effect curves obtained for the tested U937 cell line (histiocytic lymphoma and/or myeloid) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0044] FIG. 29 illustrates the dose-effect curves obtained for the tested K562 cell line (leukemia, myeloid, and/or chronic myelogenous leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0045] FIG. 30 illustrates the dose-effect curves obtained for the tested Daudi cell line (human Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0046] FIG. 31 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB and/or PTCL) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0047] FIG. 32 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Rec-1 (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 34, FIG. 35, FIG. 36, and FIG. 37.

[0048] FIG. 33 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Rec-1 (follicular lymphoma). All corresponding CIs are shown for each of the combinations tested as listed on the x axis.

[0049] FIG. 34 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB or PTCL) cell line using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0050] FIG. 35 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0051] FIG. 36 illustrates the dose-effect curves obtained for the tested HBL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0052] FIG. 37 illustrates the dose-effect curves obtained for the tested Rec-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the PI3K-δ inhibitor of Formula (IX) ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[0053] FIG. 38 illustrates tumor growth suppression in an orthotopic pancreatic cancer model. Mice were dosed orally with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K-δ inhibitor of Formula (IX), or a combination of both drugs. The statistical p-value (presumption against null hypothesis) is shown for each tested single agent and for the combination against the vehicle.

[0054] FIG. 39 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K-δ inhibitor of Formula (IX), or a combination of both inhibitors on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice.

[0055] FIG. 40 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K-δ inhibitor of Formula (IX), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice.

[0056] FIG. 41 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K-δ inhibitor of Formula (IX), or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice.

DETAILED DESCRIPTION OF THE INVENTION

[0057] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

[0058] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[0059] The terms "co-administration" and "administered in combination with" as used herein, encompass administration of two or more agents to a subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0060] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, *etc.* which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0061] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0062] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In selected embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0063] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

[0064] "Prodrug" is intended to describe a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers the advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgaard, H., Design of Prodrugs (1985) (Elsevier, Amsterdam). The term "prodrug" is also intended to include any covalently bonded carriers, which release the active compound *in vivo* when administered to a subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to yield the active parent compound. Prodrugs include, for example, compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetates, formates and benzoate derivatives of an alcohol, various ester derivatives of a carboxylic acid, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound.

[0065] The term "*in vivo*" refers to an event that takes place in a subject's body.

[0066] The term "*in vitro*" refers to an event that takes places outside of a subject's body. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

[0067] Unless otherwise stated, the chemical structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds where one or more hydrogen atoms is replaced by deuterium or tritium, or wherein one or more carbon atoms is replaced by ^{13}C- or ^{14}C-enriched carbons, are within the scope of this invention.

[0068] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that "consist of" or "consist essentially of" the described features.

[0069] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C_1-C_{10} alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl and decyl. The alkyl moiety may be attached to the rest of the molecule by a single bond, such as for example, methyl (Me), ethyl (Et), n-propyl (Pr), 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$ where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0070] "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0071] "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0072] "Alkylheterocycloalkyl" refers to an -(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

[0073] An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0074] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, C_2-C_{10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkenyl moiety may be attached to the rest of the molecule by a single bond, such as for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl and penta-1,4-dienyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0075] "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cyclo alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

[0076] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e. C_2-C_{10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0077] "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

[0078] "Carboxaldehyde" refers to a -(C=O)H radical.

[0079] "Carboxyl" refers to a -(C=O)OH radical.

[0080] "Cyano" refers to a -CN radical.

[0081] "Cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (i.e. C_2-C_{10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - *e.g.*, "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloseptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is

1 or 2), -S(O)$_t$N(R^a)$_2$ (where t is 1 or 2), or PO$_3$(R^a)$_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0082] "Cycloalkyl-alkenyl" refers to a -(cycloalkyl)alkenyl radical where cycloalkyl and alkenyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkenyl, respectively.

[0083] "Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl)heterocycloalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heterocycloalkyl, respectively.

[0084] "Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heteroaryl, respectively.

[0085] The term "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy and cyclohexyloxy. "Lower alkoxy" refers to alkoxy groups containing one to six carbons.

[0086] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (*i.e.*, -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)$_2$, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)$_2$, -C(O)N(R^a)$_2$, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)$_2$, N(R^a)C(NR^a)N(R^a)$_2$, -N(R^a)S(O)$_t$R^a (where t is 1 or 2), -S(O)$_t$OR^a (where t is 1 or 2), -S(O)$_t$N(R^a)$_2$ (where t is 1 or 2), or PO$_3$(R^a)$_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0087] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C_1-C_6 alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group.

[0088] The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0089] "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)- and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the alkyl, aryl or heteroaryl moiety of the acyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0090] "Acyloxy" refers to a R(C=O)O- radical wherein "R" is alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl, which are as described herein. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0091] "Amino" or "amine" refers to a $-N(R^a)_2$ radical group, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a $-N(R^a)_2$ group has two R^a substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, $-N(R^a)_2$ is intended to include, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0092] The term "substituted amino" also refers to N-oxides of the groups $-NHR^d$, and NR^dR^d each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid.

[0093] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R)_2$ or $-NHC(O)R$, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The R_2 of $-N(R)_2$ of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound of Formula (I), thereby forming a prodrug. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

[0094] "Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms (*e.g.*, C_6-C_{10} aromatic or C_6-C_{10} aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group may consist of 6 ring atoms, 7 ring atoms, *etc.*, up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0095] "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl-radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0096] "Ester" refers to a chemical radical of formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The procedures and specific groups to make esters are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0097] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

[0098] "Halo", "halide", or, alternatively, "halogen" is intended to mean fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

[0099] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given - *e.g.*, C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00100] "Heteroalkylaryl" refers to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl, respectively.

[00101] "Heteroalkylheteroaryl" refers to an -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl, respectively.

[00102] "Heteroalkylheterocycloalkyl" refers to an -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl, respectively.

[00103] "Heteroalkylcycloalkyl" refers to an -(heteroalkyl)cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl, respectively.

[00104] "Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (*e.g.*, C_5-C_{13} heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range - *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical - *e.g.*, a pyridyl group with two points of attachment is a pyridylidene. A N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl(benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00105] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl N-oxides.

[00106] "Heteroarylalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

[00107] "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range - *e.g.*, "3 to 18 ring atoms" means that the heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, *etc.*, up to and including 18 ring atoms. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, 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, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00108] "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

[00109] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - *i.e.*, having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[00110] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which may potentially have an (R)- or an (S)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (R)- or (S)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (S)- and 20% (R)-, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or the Pirkle alcohol, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[00111] "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00112] "Nitro" refers to the $-NO_2$ radical.

[00113] "Oxa" refers to the -O- radical.

[00114] "Oxo" refers to the =O radical.

[00115] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[00116] The terms "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (R)-enantiomer, such as at least 75% by weight, such as at least 80% by weight. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, such as at least 90% by weight, such as at least 95% by weight.

[00117] In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); and E. L. Eliel, Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962).

[00118] A "leaving group or atom" is any group or atom that will, under selected reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Examples of such groups, unless otherwise specified, include halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[00119] "Protecting group" is intended to mean a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and the group can then be readily removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999).

[00120] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[00121] "Substituted" means that the referenced group may have attached one or more additional moieties individually and independently selected from, for example, acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and protected derivatives thereof. The substituents themselves may be substituted, for example, a cycloalkyl substituent may itself have a halide substituent at one or more of its ring carbons.

[00122] "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

[00123] "Sulfinyl" refers to groups that include -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl) and -S(O)-(optionally substituted heterocycloalkyl).

[00124] "Sulfonyl" refers to groups that include -S(O_2)-H, -S(O_2)-(optionally substituted alkyl), -S(O_2)-(optionally substituted amino), -S(O_2)-(optionally substituted aryl), -S(O_2)-(optionally substituted heteroaryl), and -S(O_2)-(optionally substituted heterocycloalkyl).

[00125] "Sulfonamidyl" or "sulfonamido" refers to a -S(=O)$_2$-NRR radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in -NRR of the -S(=O)$_2$-NRR radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[00126] "Sulfoxyl" refers to a -S(=O)$_2$OH radical.

[00127] "Sulfonate" refers to a -S(=O)$_2$-OR radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[00128] Compounds of the invention also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" are intended to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to.

Co-administration of compounds

[00129] An aspect of the invention is a composition, such as a pharmaceutical composition, comprising a combination of a PI3K inhibitor and a BTK inhibitor.

[00130] Another aspect of the invention is a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination of a PI3K inhibitor and a BTK inhibitor.

[00131] In an exemplary embodiment, the PI3K inhibitor is a PI3K-γ inhibitor.

[00132] In an exemplary embodiment, the PI3K inhibitor is a PI3K-δ inhibitor.

[00133] In an exemplary embodiment, the PI3K inhibitor is a PI3K-γ,δ inhibitor.

[00134] In an exemplary embodiment, the PI3K inhibitor is a selective PI3K inhibitor.

[00135] In an exemplary embodiment, the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers.

[00136] In an exemplary embodiment, the leukemia is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL).

[00137] In an exemplary embodiment, the combination of the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor with the BTK inhibitor is administered by intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

[00138] In an exemplary embodiment, the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is in the form of a pharmaceutically acceptable salt.

[00139] In an exemplary embodiment, the BTK inhibitor is in the form of a pharmaceutically acceptable salt.

[00140] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is administered to the subject before administration of the BTK inhibitor.

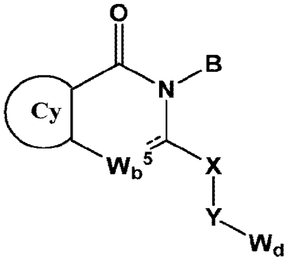
[00141] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is administered concurrently with the administration of the BTK inhibitor.

[00142] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, PI3K-γ,δ inhibitor is administered to the subject after administration of the BTK inhibitor.

[00143] In an exemplary embodiment, the subject is a mammal, such as a human.

PI3K Inhibitors

[00144] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 8,193,182 and 8,569,323, and U.S. Patent Application Publication Nos. 2012/0184568 A1, 2013/0344061 A1, and 2013/0267521 A1, the disclosures of which are incorporated by reference herein. In an exemplary embodiment, the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

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

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

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

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

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

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

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

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

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

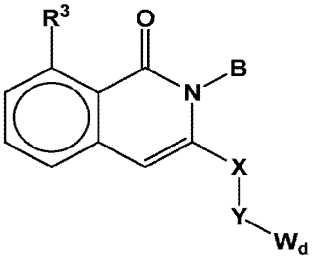
each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

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

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

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

[00145] In an exemplary embodiment, the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (I-1):

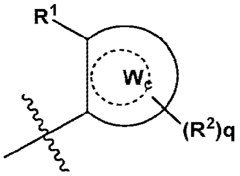


Formula (I-1)

or a pharmaceutically acceptable salt thereof,

wherein:

B is a moiety of Formula (II):



Formula (II) ;

W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

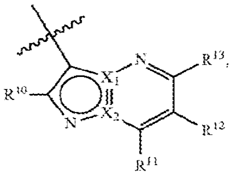
q is an integer of 0, 1, 2, 3, or 4;

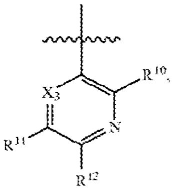
X is a bond or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3 or 4;

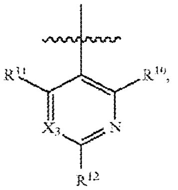
Y is a bond, $-N(R^9)-$, -O-, -S-, -S(=O)-, $-S(=O)_2$, -C(=O)-, $-C(=O)(CHR^9)_z-$, $-N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$ or $-N(R^9)C(R^9)_2-$;

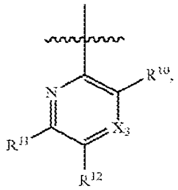
z is an integer of 1, 2, 3, or 4;

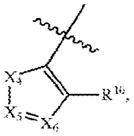
W_d is:

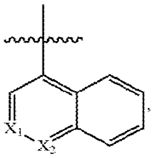

X1
X2
N
N
R10
R13,
R12
R11

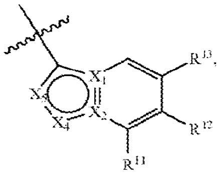

X3
N
R10,
R11
R12

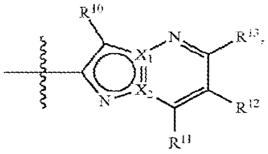

R11
R10,
X3
N
R12

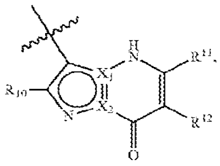

N
X3
R10,
R11
R12

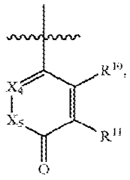

X4
X5
X6
R10,

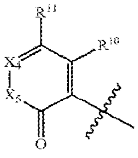

X1
X2


X1
X2
X3
X4
R13,
R12
R11


R10
X1
X2
N
N
R13,
R12
R11







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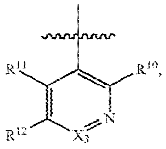
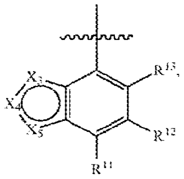
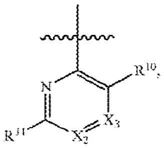
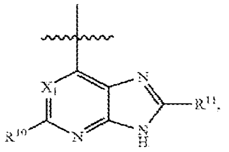
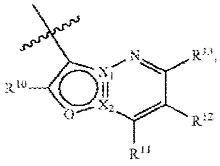
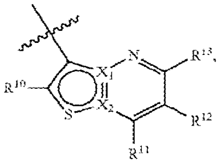


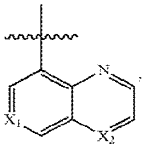




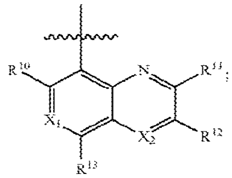








, or



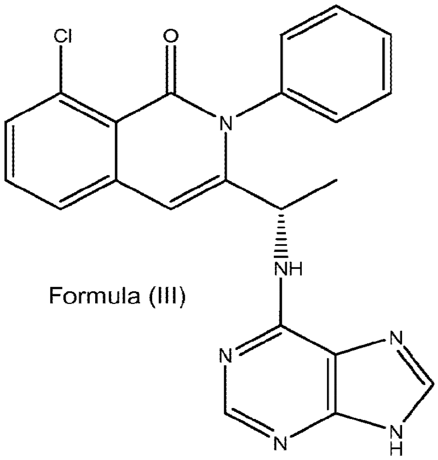
X_1, X_2 and X_3 are each independently C, CR^{13} or N; and X_4, X_5 and X_6 are each independently N, NH, CR^{13}, S or O;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

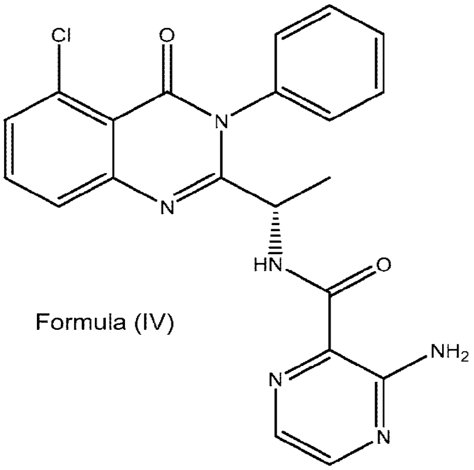
R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; R.sup.3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy or nitro; and

each instance of R^9 is independently hydrogen, alkyl, or heterocycloalkyl.

[00146] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (III) or Formula (IV):



Formula (III)



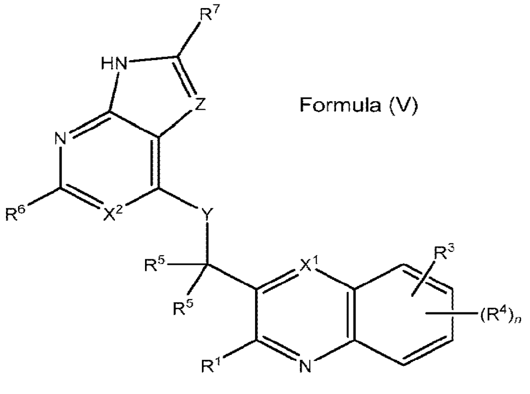
Formula (IV)

or a pharmaceutically acceptable salt thereof.

[00147] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is (S)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one or a pharmaceutically acceptable salt thereof.

[00148] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is (S)-3-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide or a pharmaceutically acceptable salt thereof.

[00149] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 8,193,199 and 8,586,739, the disclosure of which is incorporated by reference herein. In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (V):



Formula (V)

or any pharmaceutically-acceptable salt thereof, wherein:

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

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

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

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one 0 or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1_4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}, $N(C_{1-4}$alkyl)C_{1-4}alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a. —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, OS(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6} alkylNR^aR^a and —NR^aC_{2-6}alkylOR^a; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C_{1-3}alkyl)heteroaryl, —(C_{1-3}alkyl)heterocycle, —O(C_{1-3}alkyl)heteroaryl, —O(C_{1-3}alkyl)heterocycle, —NR^a(C_{1-3}alkyl)heteroaryl, —NR^a(C_{1-3}alkyl)heterocycle, —(C_{1-3}alkyl)phenyl, —O(C_{1-3}alkyl)phenyl and —NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)R^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^2$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aNR^aR^a, —NR^aC_{2-6}alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

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

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

R^6 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

R^7 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

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

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^aC(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(O)N$R^aR^aR^a$N(R^aC(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6} alkylNR^aR^a, —NR^aC_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6}alkylOR^a, —NR^aC_{2-6}alkylOR^a; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —

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

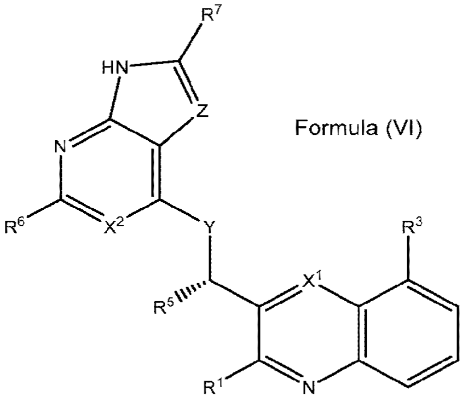
R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $—C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, $—S(=O)_2N(R^a)C(=O)OR^a$, $—S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

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

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

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

[00150] In another exemplary embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VI):



Formula (VI)

or any pharmaceutically-acceptable salt thereof, wherein:

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

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

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

Z is CR^8 or N;

n is 0, 1, 2 or 3;

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

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —N$R^a$$C_{2-6}$ alkylNR^aR^a and —N$R^a$$C_{2-6}$alkylO$R^a$; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C_{1-3}alkyl)heteroaryl, —(C_{1-3}alkyl)heterocycle, —O(C_{1-3}alkyl)heteroaryl, —O(C_{1-3}alkyl)heterocycle, —NR^a(C_{1-3}alkyl)heteroaryl, —NR^a(C_{1-3}alkyl)heterocycle, —(C_{1-3}alkyl)phenyl, —O(C_{1-3}alkyl)phenyl and —NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, C(=O)NR^aR^aC(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —N$R^a$$C_{2-6}$alkylO$R^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

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

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl,

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

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

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

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

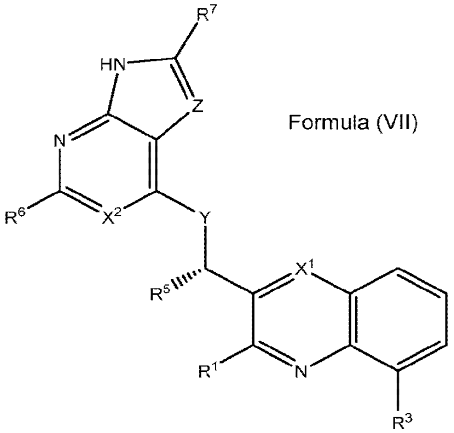
R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, OC(=O)NR^aR^a, —$OC(=O)N(R^a)S(=O)_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$,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

R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$; —R^{11} is H or C_{1-4}alkyl;

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

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

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



Formula (VII)

or any pharmaceutically-acceptable salt thereof, wherein:

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

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

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

Z is CR^8 or N;

n is 0, 1, 2 or 3;

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

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

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

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

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

R^6 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —S(=O)R^{a}S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a;

R^7 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —S(=O)R^{a}S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a;

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

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC_{2-6}alkylNR^{a}R^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —NR^aC_{2-6}alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^8, —OC(=O)R^8, —OC(=O)NR^{2}R^8, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC_{2-6}alkylNR^{a}R^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^8, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —

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

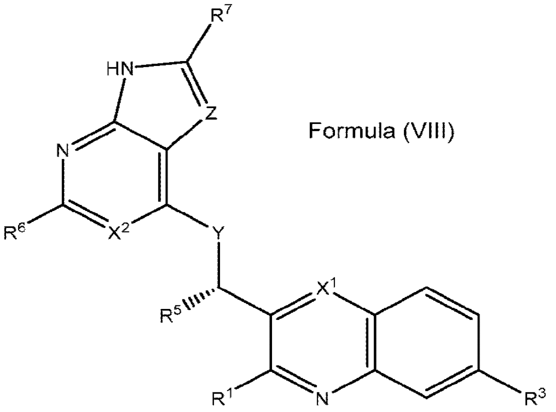
R^{10} is H, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $—C(=NR^a)NR^aR^a$, $—S(=O)_2N(R^a)C(=O)R^a$, $—S(=O)_2N(R^a)C(=O)OR^a$, $—S(=O)_2N(R^a)C(=O)NR^aR^a$, $—S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

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

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

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

[00152] In another exemplary embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VIII):



Formula (VIII)

or any pharmaceutically-acceptable salt thereof, wherein:

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

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

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

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C$_{1\text{-}4}$alkyl, OC$_{1\text{-}4}$alkyl, OC$_{1\text{-}4}$haloalkyl, NHC$_{1\text{-}4}$alkyl, N(C$_{1\text{-}4}$ alkyl)C$_{1\text{-}4}$alkyl and C$_{1\text{-}4}$haloalkyl;

R^2 is selected from halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a—C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —NR^{a}C$_{2\text{-}6}$ alkylNR^{a}R^a and —NR^{a}C$_{2\text{-}6}$alkylOR^a; or R^2 is selected from C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C$_{1\text{-}3}$alkyl)heteroaryl, —(C$_{1\text{-}3}$alkyl)heterocycle, —O(C$_{1\text{-}3}$ alkyl)heteroaryl, —O(C$_{1\text{-}3}$alkyl)heterocycle, —NR^a(C$_{1\text{-}3}$alkyl)heteroaryl, —NR^a(C$_{1\text{-}3}$ alkyl)heterocycle, —(C$_{1\text{-}3}$alkyl)phenyl, —O(C$_{1\text{-}3}$alkyl)phenyl and —NR^a(C$_{1\text{-}3}$alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C$_{1\text{-}4}$haloalkyl, OC$_{1\text{-}4}$alkyl, Br, Cl, F, I and C$_{1\text{-}4}$alkyl;

R^3 is selected from H, halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a—C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}NR^a, —

NR^a, —NR^{a}C$_{2\text{-}6}$alkylOR^a, C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C$_{1\text{-}6}$haloalkyl, OC$_{1\text{-}6}$alkyl, Br, Cl, F, I and C$_{1\text{-}6}$alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C$_{1\text{-}4}$alkyl, OC$_{1\text{-}4}$alkyl, OC$_{1\text{-}4}$haloalkyl, NHC$_{1\text{-}4}$alkyl, N(C$_{1\text{-}4}$alkyl)C$_{1\text{-}4}$alkyl or C$_{1\text{-}4}$haloalkyl;

R^5 is, independently, in each instance, H, halo, C$_{1\text{-}6}$alkyl, C$_{1\text{-}4}$haloalkyl, or C$_{1\text{-}6}$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC$_{1\text{-}4}$alkyl, C$_{1\text{-}4}$alkyl, C$_{1\text{-}3}$haloalkyl, OC$_{1\text{-}4}$alkyl, NH$_2$, NHC$_{1\text{-}4}$alkyl, N(C$_{1\text{-}4}$alkyl)C$_{1\text{-}4}$alkyl; or both R^5 groups together form a C$_{3\text{-}6}$-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC$_{1\text{-}4}$alkyl, C$_{1\text{-}4}$alkyl, C$_{1\text{-}3}$haloalkyl, OC$_{1\text{-}4}$alkyl, NH$_2$, NHC$_{1\text{-}4}$alkyl, N(C$_{1\text{-}4}$alkyl)C$_{1\text{-}4}$alkyl;

R^6 is selected from H, halo, C$_{1\text{-}6}$alkyl, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a;

R^7 is selected from H, halo, C$_{1\text{-}6}$alkyl, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a;

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

R^9 is selected from H, halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylNR^{a}R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —NR^{a}C$_{2\text{-}6}$alkylNR^{a}R^a, —NR^{a}C$_{2\text{-}6}$alkylOR^a, C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, —S(=O)R^a, —

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

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

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

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

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

[00153] In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $C(R^9)$ and X^2 is N.

[00154] In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $C(R^9)$ and X^2 is $C(R^{10})$.

[00155] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl substituted by 0 or 1 R^2 substituents, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}$alkyl$)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00156] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl.

[00157] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl substituted by R^2, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00158] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is selected from 2-methylphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-fluorophenyl and 2-methoxyphenyl.

[00159] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenoxy.

[00160] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00161] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00162] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or

1 R^2 substituents, and the ring is additionally substituted by 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00163] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S.

[00164] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is selected from pyridyl and pyrimidinyl.

[00165] In another embodiment, in conjunction with any of the above or below embodiments, R^3 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —$C(O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}alkylNR^aR^a$, —$OC_{2-6}alkylOR^a$, —SR^a, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}alkylNR^aR^a$, —$NR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl.

[00166] In another embodiment, in conjunction with any of the above or below embodiments, R^3 is H.

[00167] In another embodiment, in conjunction with any of the above or below embodiments, R^3 is selected from F, Cl, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl.

[00168] In another embodiment, in conjunction with any of the above or below embodiments, R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-}

$_6$spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC$_{1-4}$alkyl, C$_{1-4}$alkyl, C$_{1-3}$haloalkyl, OC$_{1-4}$alkyl, NH$_2$, NHC$_{1-4}$alkyl, N(C$_{1-4}$alkyl)C$_{1-4}$alkyl.

[00169] In another embodiment, in conjunction with any of the above or below embodiments, R^5 is H.

[00170] In another embodiment, in conjunction with any of the above or below embodiments, one R^5 is S-methyl, the other is H.

[00171] In another embodiment, in conjunction with any of the above or below embodiments, at least one R^5 is halo, C$_{1-6}$alkyl, C$_{1-4}$haloalkyl, or C$_{1-6}$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC$_{1-4}$alkyl, C$_{1-4}$alkyl, C$_{1-3}$haloalkyl, OC$_{1-4}$alkyl, NH$_2$, NHC$_{1-4}$alkyl, N(C$_{1-4}$alkyl)C$_{1-4}$alkyl.

[00172] In another embodiment, in conjunction with any of the above or below embodiments, R^6 is H.

[00173] In another embodiment, in conjunction with any of the above or below embodiments, R^6 is F, Cl, cyano or nitro.

[00174] In another embodiment, in conjunction with any of the above or below embodiments, R^7 is H.

[00175] In another embodiment, in conjunction with any of the above or below embodiments, R^7 is F, Cl, cyano or nitro.

[00176] In another embodiment, in conjunction with any of the above or below embodiments, R^8 is selected from H, CF$_3$, C$_{1-3}$alkyl, Br, Cl and F.

[00177] In another embodiment, in conjunction with any of the above or below embodiments, R^8 is selected from H.

[00178] In another embodiment, in conjunction with any of the above or below embodiments, R^8 is selected from CF$_3$, C$_{1-3}$alkyl, Br, Cl and F.

[00179] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is H.

[00180] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is selected from halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylNR^{a}R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —NR^{a}C$_{2\text{-}6}$alkylNR^{a}R^a, —NR^{a}C$_{2\text{-}6}$alkylOR^a, C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —NR^{a}C$_{2\text{-}6}$alkylNR^{a}R^a, —NR^{a}C$_{2\text{-}6}$alkylOR^a.

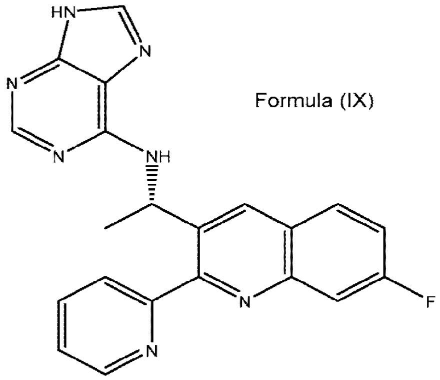
[00181] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylNR^{a}R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —NR^{a}C$_{2\text{-}6}$alkylNR^{a}R^a and —NR^{a}C$_{2\text{-}6}$alkylOR^a.

[00182] In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is H.

[00183] In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $—C(=NR^a)NR^aR^a$, $—S(=O)_2N(R^a)C(=O)R^a$, $—S(=O)_2N(R^a)C(=O)OR^a$, $—S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$.

[00184] In another embodiment, in conjunction with any of the above or below embodiments, R^{11} is H.

[00185] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (IX):

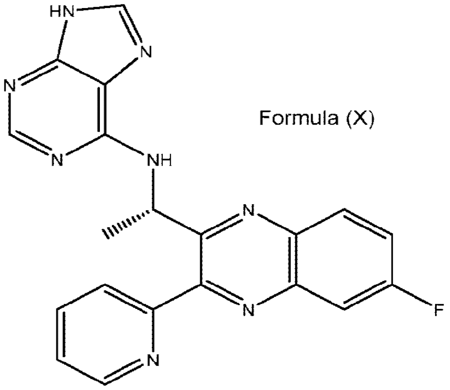


Formula (IX)

or a pharmaceutically-acceptable salt thereof

[00186] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00187] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (X):

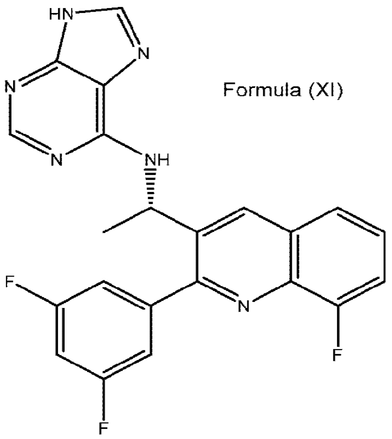


Formula (X)

or a pharmaceutically-acceptable salt thereof

[00188] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(6-fluoro-3-(pyridin-2-yl)quinoxalin-2-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00189] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XI):

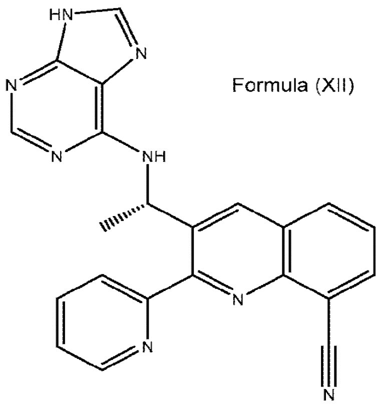


Formula (XI)

or a pharmaceutically-acceptable salt thereof.

[00190] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(2-(3,5-difluorophenyl)-8-fluoroquinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00191] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XII):

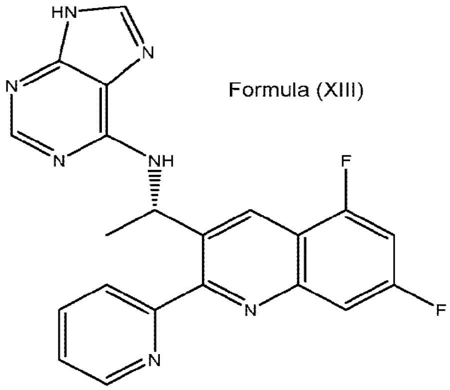


Formula (XII)

or a pharmaceutically-acceptable salt thereof

[00192] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-2-(pyridin-2-yl)quinoline-8-carbonitrile or a pharmaceutically-acceptable salt thereof.

[00193] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XIII):



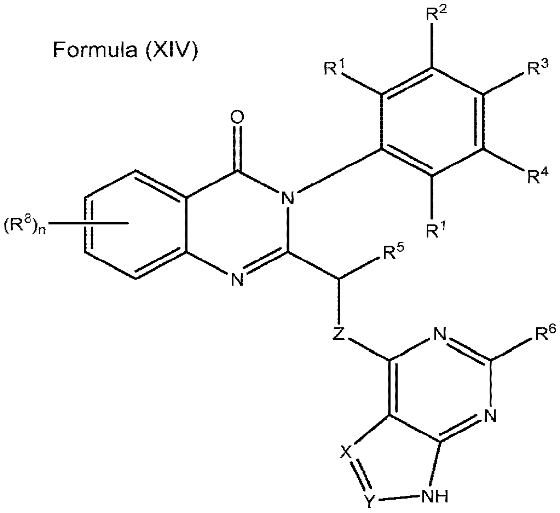
Formula (XIII)

or a pharmaceutically-acceptable salt thereof

[00194] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(5,7-difluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00195] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 7,932,260 and 8,207,153, the disclosure of which is incorporated by reference herein. In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XIV):

Formula (XIV)



wherein

X and Y, independently, are N or CRC;

Z is N—R^7 or O;

R^1 are the same and are hydrogen, halo, or $C_{1\text{-}3}$alkyl;

R^2 and R^3, independently, are hydrogen, halo, or $C_{1\text{-}3}$alkyl;

R^4 is hydrogen, halo, OR^a, CN, $C_{2\text{-}6}$alkynyl, $C(=O)R^a$, $C(=O)NR^aR^b$, $C_{3\text{-}6}$heterocycloalkyl, $C_{1\text{-}3}$ alkylene$C_{3\text{-}6}$heterocycloalkyl, $OC_{1\text{-}3}$alkyleneOR^a, $OC_{1\text{-}3}$alkyleneNR^aR^b, $OC_{1\text{-}3}$alkylene$C_{3\text{-}6}$ cycloalkyl, $OC_{3\text{-}6}$heterocycloalkyl, $OC_{1\text{-}3}$alkylene$C\equiv CH$, or $OC_{1\text{-}3}$alkylene$C(=O)NR^aR^b$;

R^5 is $C_{1\text{-}3}$alkyl, CH_2CF_3, phenyl, $CH_2C\equiv CH$, $C_{1\text{-}3}$alkyleneOR^e, $C_{1\text{-}4}$alkyleneNR^aR^b, or $C_{1\text{-}4}$ alkylene$NHC(=O)OR^a$,

R^6 is hydrogen, halo, or NR^aR^b;

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

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

n is 0, 1, or 2;

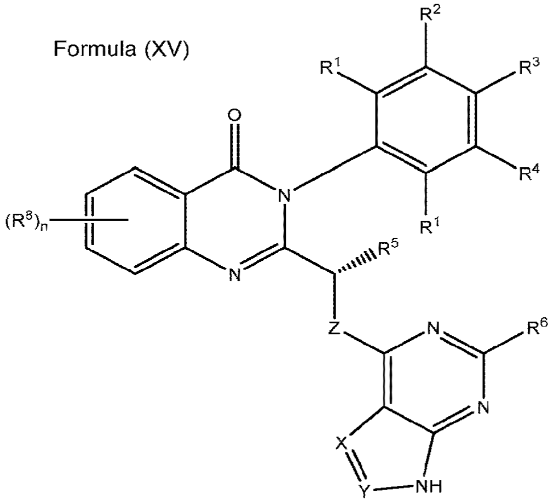
R^a is hydrogen, C_{1-4}alkyl, or $CH_2C_6H_5$;

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

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

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

[00196] In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is an enantiomer of Formula (XIV), as shown in Formula (XV):



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

[00197] In various embodiments exhibiting increased potency relative to other compounds, R^8 is C_{1-3}alkyl, F, Cl, or CF_3. Alternatively, in such embodiments, n is 0 (such that there is no R^8 substituent).

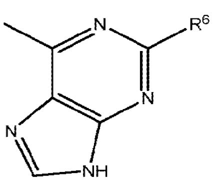
[00198] In other embodiments exhibiting such increased potency, X and Y, independently, are N or CH. In further embodiment exhibiting increased potency, X is N and Y is CH.

Alternatively, X and Y may also both be CH. In further embodiments exhibiting increased potency, R^6 is hydrogen, halo, or NH_2.

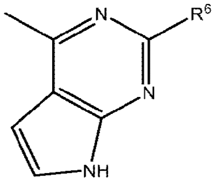
[00199] Unexpectedly, potency against PI3K-δ is conserved when R^1 is the same. In structural formulae (I) and (II), R^2 and R^4 may differ provided that R^1 is H. When R^1 is H, free rotation is unexpectedly permitted about the bond connecting the phenyl ring substituent to the quinazoline ring, and the compounds advantageously do not exhibit atropisomerism (i.e., multiple diasteromer formation is avoided). Alternatively, R^2 and R^4 can be the same such that the compounds advantageously do not exhibit atropisomerism.

[00200] As used with respect to Formula (XIV) and Formula (XV), the term "alkyl" is defined as straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms, e.g., methyl, ethyl, and straight chain and branched propyl and butyl groups. The terms "$C_{1\text{-}3}$alkylene" and "$C_{1\text{-}4}$alkylene" are defined as hydrocarbon groups containing the indicated number of carbon atoms and one less hydrogen than the corresponding alkyl group. The term "$C_{2\text{-}6}$alkynyl" is defined as a hydrocarbon group containing the indicated number of carbon atoms and a carbon-carbon triple bond. The term "$C_{3\text{-}6}$cycloalkyl" is defined as a cyclic hydrocarbon group containing the indicated number of carbon atoms. The term "$C_{2\text{-}6}$heterocycloalkyl" is defined similarly as cycloalkyl except the ring contains one or two heteroatoms selected from the group consisting of O, NR^a, and S. The term "halo" is defined as fluoro, bromo, chloro, and iodo.

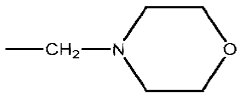
[00201] In preferred embodiments, Z is N—R^7, and the bicyclic ring system containing X and Y is:



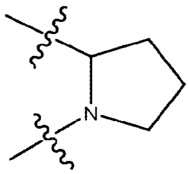
or



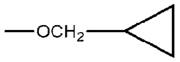
[00202] In other preferred embodiments, R^1 is hydrogen, fluoro, chloro, methyl, or



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



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



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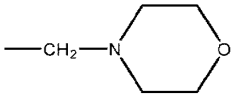

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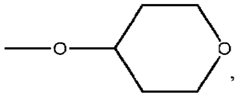
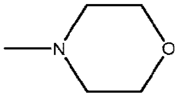
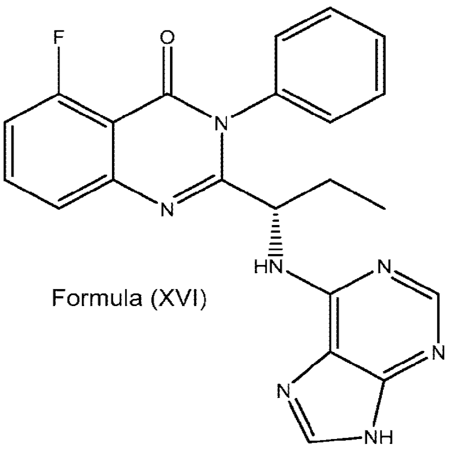


, or



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

[00203] In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is the compound of Formula (XVI):



Formula (XVI)

or a pharmaceutically-acceptable salt thereof.

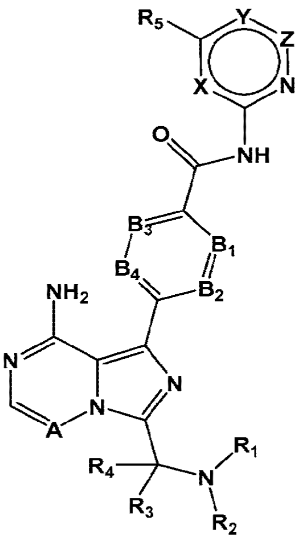
[00204] In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one or a pharmaceutically-acceptable salt thereof.

[00205] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is 4(3*H*)-quinazolinone, 5-fluoro-3-phenyl-2-[(1*S*)-1-(9*H*-purin-6-ylamino)propyl]-5-fluoro-3-phenyl-2-{(1*S*)-1-[(7*H*-purin-6-yl)amino]propyl}quinazolin-4(3*H*)-one or or a pharmaceutically-acceptable salt thereof

[00206] Other PI3K inhibitors suitable for use in the described combination with a BTK inhibitor also include, but are not limited to, those described in, for example, U.S. Patent No. 8,193,182 and U.S. Published Application Nos. 2013/0267521; 2013/0053362; 2013/0029984; 2013/0029982; 2012/0184568; and 2012/0059000, the disclosures of each of which are incorporated by reference in their entireties.

BTK Inhibitors

[00207] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XVII):



Formula (XVII)

or a pharmaceutically acceptable salt thereof,

wherein:

X is CH, N, O or S;

Y is C(R_6), N, O or S;

Z is CH, N or bond;

A is CH or N;

B_1 is N or C(R_7);

B_2 is N or C(R_8);

B_3 is N or C(R_9);

B_4 is N or C(R_{10});

R_1 is $R_{11}C(=O)$, $R_{12}S(=O)$, $R_{13}S(=O)_2$ or (1-6C)alkyl optionally substituted with R_{14};

R_2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R_3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R_2 and R_3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R_4 is H or (1-3C)alkyl;

R_5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R_5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R_6 is H or (1-3C)alkyl; or

R_5 and R_6 together may form a (3-7C)cycloalkenyl or (2-6C)heterocycloalkenyl, each optionally substituted with (1-3C)alkyl or one or more halogens;

R_7 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy;

R_8 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy; or

R_7 and R_8 together with the carbon atoms they are attached to, form (6-10C)aryl or (1-9C)heteroaryl;

R_9 is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{10} is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{11} is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl, where each alkyl, alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl; or R_{11} is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

R_{11} is (1-5C)heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen or cyano;

R_{12} and R_{13} are independently selected from the group consisting of (2-6C)alkenyl or (2-6C)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl; or a (1-5C)heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen and cyano; and

R_{14} is independently selected from the group consisting of halogen, cyano, (2-6C)alkenyl and (2-6C)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl and (3-7C)heterocycloalkyl;

with the proviso that:

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

when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;

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

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

with the terms used having the following meanings:

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

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

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

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

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

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

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

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

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

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

(2-6C)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl. (2-4C)alkynyl groups are preferred; (3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

(3-7C)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

(2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; also preferred are piperidine, morpholine, pyrrolidine and piperazine; with the most preferred (2-6C)heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;

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

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

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

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

(1-9C)heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (1-9C)heteroaryl may optionally be substituted; preferred (1-9C)heteroaryl groups are quinoline, isoquinoline and indole;

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

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

halogen means means fluorine, chlorine, bromine or iodine;

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

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

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

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

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

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

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

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

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

[00208] In an exemplary embodiment of Formula (XVII), B_1 is $C(R_7)$; B_2 is $C(R_8)$; B_3 is $C(R_9)$; B_4 is $C(R_{10})$; R_7, R_9, and R_{10} are each H; and R_8 is hydrogen or methyl.

[00209] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

[00210] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyridazyl.

[00211] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

[00212] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is pyridyl.

[00213] In an exemplary embodiment of Formula (XVII), R_5 is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

[00214] In an exemplary embodiment of Formula (XVII), R_5 is hydrogen.

[00215] In an exemplary embodiment of Formula (XVII), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl and morpholinyl, optionally substituted with one or more of fluoro, hydroxyl, (1-3C)alkyl and (1-3C)alkoxy.

[00216] In an exemplary embodiment of Formula (XVII), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

[00217] In an exemplary embodiment of Formula (XVII), R_2 and R_3 together form a pyrrolidinyl ring.

[00218] In an exemplary embodiment of Formula (XVII), R_1 is independently selected from the group consisting of (l-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-

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

[00219] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X is N; Y and Z are CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

[00220] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

[00221] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-ethenyl.

[00222] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is H; A is CH; R_2 and R_3 together form a pyrrolidinyl ring; R_4 is H; and R_1 is CO-propynyl.

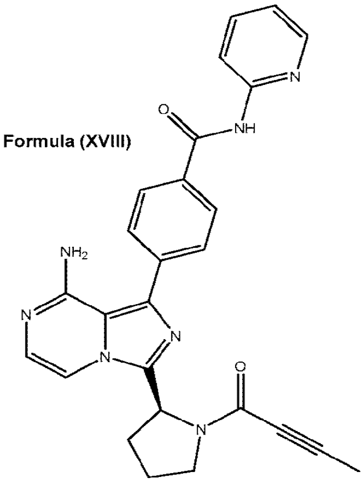
[00223] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-propynyl.

[00224] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is H; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-ethenyl.

[00225] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-propynyl.

[00226] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XVIII):

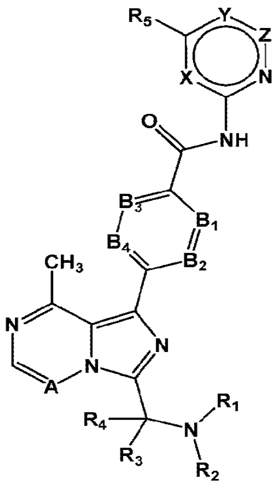
Formula (XVIII)



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

[00227] In an exemplary embodiment, the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or pharmaceutically-acceptable salt therof.

[00228] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XIX) or a pharmaceutically-acceptable salt of a compound of Formula (XIX):



Formula (XIX)

In Formula (XIX) the substituents are defined as

X is CH, N, O or S;

Y is C(R_6), N, O or S;

Z is CH, N or bond;

A is CH or N;

B_1 is N or C(R_7);

B_2 is N or C(R_8);

B_3 is N or C(R_9);

B_4 is N or C(R_{10});

R_1 is R_{11}C(0), R_{12}S(O), $R_{13}SO_2$ or (1-6C)alkyl optionally substituted with R_{14};

R_2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R_3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R_2 and R_3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R_4 is H or (1-3C)alkyl;

R_5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl; all alkyl groups of R5 are optionally substituted with one or more halogen; or R_5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R_6 is H or (1-3C)alkyl; or R_5 and R_6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R_7 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy;

R_8 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy; or

R_7 and R_8 together with the carbon atoms they are attached to, form (6-10C)aryl or (1-5C)heteroaryl;

R_9 is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{10} is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{11} is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl, or

R_{11} is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

R_{11} is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

R_{12} and R_{13} are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, or (3-7C)heterocycloalkyl; or

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

R_{14} is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
- when Z is C or N then Y is C(R_6) or N and X is C or N;
- 0 to 2 atoms of B_1, B_2, B_3 and B_4 are N;

with the terms used having the following meanings:

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

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

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

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

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

(2-3C)alkenyl means an alkenyl group having 2-3 carbon atoms, such as ethenyl or 2- propenyl;

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

(2-6C)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, with (2-4C)alkenyl groups preferred, and (2-3C)alkenyl groups even more preferred;

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

(2-3C)alkynyl means an alkynyl group having 2-3 carbon atoms, such as ethynyl or 2-propynyl;

(2-6C)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl, wtih (2-4C)alkynyl groups preferred, and (2-3C)alkynyl groups more preferred;

(3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

(3-7C)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

(2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3- 5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O;

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

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

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

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

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

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

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

halogen means means fluorine, chlorine, bromine or iodine;

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

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

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

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

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

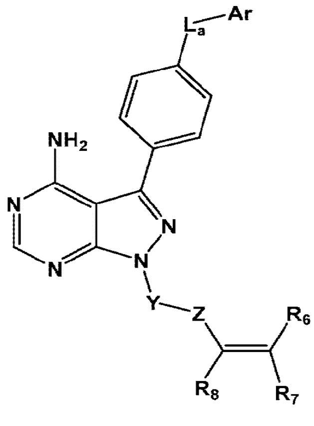
A circle in a ring of Formula (XIX) indicates that the ring is aromatic.

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

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

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties. In one aspect the invention relates to a compound according to formula I wherein B_1 is $C(R_7)$; B_2 is $C(R_8)$; B_3 is $C(R_9)$ and B_4 is $C(R_{10})$.

[00229] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XX):



Formula (XX)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2, O, NH or S;

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

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

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

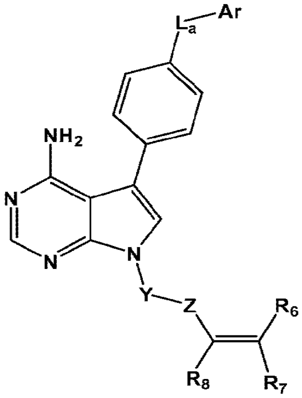
R^7 and R^8 are each independently H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

R is H or C_1-C_6alkyl.

[00230] In an exemplary embodiment, the BTK inhibitor is ibrutinib or a pharmaceutically-acceptable salt thereof.

[00231] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXI):



Formula (XXI)

or a pharmaceutically acceptable salt thereof,

wherein:

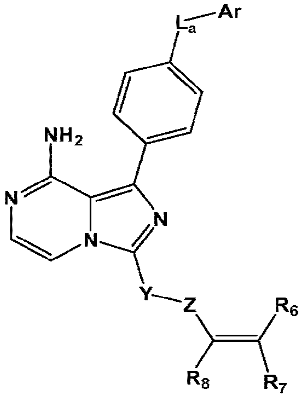
L_a is CH_2, O, NH or S;

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

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

Z is C(=O), OC(=O), NRC(=O), C(=S), S(=O)$_x$, OS(=O)$_x$ or NRS(=O)$_x$, where x is 1 or 2;
R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;
R^6 is H; and
R is H or C_1-C_6alkyl.

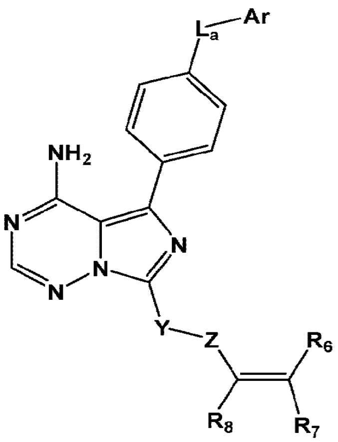
[00232] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXII):



Formula (XXII)

or a pharmaceutically acceptable salt thereof,
wherein:
L_a is CH_2, O, NH or S;
Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;
Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;
Z is C(=O), OC(=O), NRC(=O), C(=S), S(=O)$_x$, OS(=O)$_x$ or NRS(=O)$_x$, where x is 1 or 2;
R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;
R^6 is H; and
R is H or C_1-C_6alkyl.

[00233] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXIII):



Formula (XXIII)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2, O, NH or S;

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

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

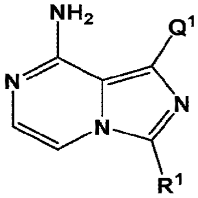
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

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

R^6 is H; and

R is H or C_1-C_6alkyl.

[00234] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXIV):



Formula (XXIV)

or a pharmaceutically acceptable salt thereof,

wherein:

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

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

G^1 and G^{41} are each independently halo, oxo, -CF$_3$, -OCF$_3$, -OR^2, -NR^{2}R^3(R^{3a})$_{j1}$, -C(O)R^2, -CO$_2$R^2, -CONR^{2}R^3, -NO$_2$, -CN, -S(O)$_{j1}$R^2, -SO$_2$NR^{2}R^3, NR^2(C=O)R^3, NR^2(C=O)OR^3, NR^2(C=O)NR^{2}R^3, NR^{2}S(O)$_{j1}$R^3, -(C=S)OR^2, -(C=O)SR^2, -NR^2(C=NR^3)NR^{2a}R^{3a}, -NR^2(C=NR^3)OR^{2a}, -NR^2(C=NR^3)SR^{3a}, -O(C=O)OR^2, -O(C=O)NR^{2}R^3, -O(C=O)SR^2, -S(C=O)OR^2, -S(C=O)NR^{2}R^3, C$_{0-10}$alkyl, C$_{2-10}$alkenyl, C$_{2-10}$alkynyl, C$_{1-10}$alkoxyC$_{1-10}$alkyl, C$_{1-10}$alkoxyC$_{2-10}$alkenyl, C$_{1-10}$alkoxyC$_{2-10}$alkynyl, C$_{1-10}$alkylthioC$_{1-10}$alkyl, C$_{1-10}$alkylthioC$_{2-10}$alkenyl, C$_{1-10}$alkylthioC$_{2-10}$alkynyl, cycloC$_{3-8}$alkyl, cycloC$_{3-8}$alkenyl, cycloC$_{3-8}$alkylC$_{1-10}$alkyl, cycloC$_{3-8}$alkenylC$_{1-10}$alkyl, cycloC$_{3-8}$alkylC$_{2-10}$alkenyl, cycloC$_{3-8}$alkenylC$_{2-10}$alkenyl, cycloC$_{3-8}$alkylC$_{2-10}$alkynyl, cycloC$_{3-8}$alkenylC$_{2-10}$alkynyl, heterocyclyl-C$_{0-10}$alkyl, heterocyclyl-C$_{2-10}$alkenyl, or heterocyclyl-C$_{2-10}$alkynyl, any of which is optionally substituted with one or more independent halo, oxo, -CF$_3$, -OCF$_3$, -OR^{222}, -NR^{222}R^{333}(R^{333}a)$_{j1a}$, -C(O)R^{222}, -CO$_2$R^{222}, -CONR^{222}R^{333}, -NO$_2$, -CN, -S(O)$_{j1a}$R^{222}, -SO$_2$NR^{222}R^{333}, NR^{222}(C=O)R^{333}, NR^{222}(C=O)OR^{333}, NR^{222}(C=O)NR^{222}R^{333}, NR^{222}S(O)$_{j1a}$R^{333}, -(C=S)OR^{222}, -(C=O)SR^{222}, -NR^{222}(C=NR^{333})NR^{222a}R^{333a}, -NR^{222}(C=NR^{333})OR^{222a}, -NR^{222}(C=NR^{333})SR^{333a}, -O(C=O)OR^{222}, -O(C=O)NR^{222}R^{333}, -O(C=O)SR^{222}, -S(C=O)OR^{222}, or -S(C=O)NR^{222}R^{333} substituents; or -(X^1)$_n$-(Y^1)$_m$-R^4; or aryl-C$_{0-10}$alkyl, aryl-C$_{2-10}$alkenyl, or aryl-C$_{2-10}$alkynyl, any of which is optionally substituted with one or more independent halo, -CF$_3$, -OCF$_3$, -OR^{222}, -NR^{222}R^{333}(R^{333a})$_{j2a}$, -C(O)R^{222}, -CO$_2$R^{222}, -CONR^{222}R^{333}, -NO$_2$, -CN, -S(O)$_{j2a}$R^{222}, -SO$_2$NR^{222}R^{333}, NR^{222}(C=O)R^{333}, NR^{222}(C=O)OR^{333}, NR^{222}(C=O)NR^{222}R^{333}, NR^{222}S(O)$_{j2a}$R^{333}, -(C=S)OR^{222}, -(C=O)SR^{222}, -NR^{222}(C=NR^{333})NR^{222a}R^{333a}, -NR^{222}(C=NR^{333})OR^{222a}, -NR^{222}(C=NR^{333})SR^{333a}, -O(C=O)OR^{222}, -O(C=O)NR^{222}R^{333}, -O(C=O)SR^{222}, -S(C=O)OR^{222}, or -S(C=O)NR^{222}R^{333} substituents; or hetaryl-C$_{0-10}$alkyl, hetaryl-C$_{2-10}$alkenyl, or hetaryl-C$_{2-10}$alkynyl, any of which is optionally substituted with one or more independent halo, -CF$_3$, -OCF$_3$, -OR^{222}, -NR^{222}, R^{333}(R^{333a})$_{j3a}$, -C(O)R^{222}, -CO$_2$R^{222}, -CONR^{222}R^{333}, -NO$_2$, -CN, -S(O)$_{j3a}$R^{222}, -SO$_2$NR^{222}R^{333},

$NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j3a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222}aR^{333}a$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333}a$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents;

G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{3a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-CONR^{21}R^{31}$, $-NO_2$, $-CN$, $-S(O)_{j4}R^{21}$, $-SO_2NR^{21}R^{31}$, $NR^{21}(C{=}O)R^{31}$, $NR^{21}(C{=}O)OR^{31}$, $NR^{21}(C{=}O)NR^{21}R^{31}$, $NR^{21}S(O)_{j4}R^{31}$, $-(C{=}S)OR^{21}$, $-(C{=}O)SR^{21}$, $-NR^{21}(C{=}NR^{31})NR^{2a1}R^{3a1}$, $-NR^{21}(C{=}NR^{31})OR^{2a1}$, $-NR^{21}(C{=}NR^{31})SR^{3a1}$, $-O(C{=}O)OR^{21}$, $-O(C{=}O)NR^{21}R^{31}$, $-O(C{=}O)SR^{21}$, $-S(C{=}O)OR^{21}$, $-S(C{=}O)NR^{21}R^{31}$, $-P(O)OR^{21}OR^{31}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C{=}O)R^{3331}$, $NR^{2221}(C{=}O)OR^{3331}$, $NR^{2221}(C{=}O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j4a}R^{3331}$, $-(C{=}S)OR^{2221}$, $-(C{=}O)SR^{2221}$, $-NR^{2221}(C{=}NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C{=}NR^{3331})OR^{222a1}$, $-NR^{2221}(C{=}NR^{3331})SR^{333a1}$, $-O(C{=}O)OR^{2221}$, $-O(C{=}O)NR^{2221}R^{3331}$, $-O(C{=}O)SR^{2221}$, $-S(C{=}O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C{=}O)NR^{2221}R^{3331}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C{=}O)R^{3331}$, $NR^{2221}(C{=}O)OR^{3331}$, $NR^{2221}(C{=}O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j5a}R^{3331}$, $-(C{=}S)OR^{2221}$, $-(C{=}O)SR^{2221}$, $-NR^{2221}(C{=}NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C{=}NR^{3331})OR^{222a1}$, $-NR^{2221}(C{=}NR^{3331})SR^{333a1}$, $-O(C{=}O)OR^{2221}$, $-O(C{=}O)NR^{2221}R^{3331}$, $-O(C{=}O)SR^{2221}$, $-S(C{=}O)OR^{2221}$, $-P(O)OR^{2221}R^{3331}$, or $-S(C{=}O)NR^{2221}R^{3331}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j6a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C{=}O)R^{3331}$, $NR^{2221}(C{=}O)OR^{3331}$,

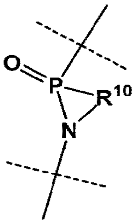
$NR^{2221}(C{=}O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j6a}R^{3331}$, $-(C{=}S)OR^{2221}$, $-(C{=}O)SR^{2221}$, $-NR^{2221}(C{=}NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C{=}NR^{3331})OR^{222a1}$, $-NR^{2221}(C{=}NR^{3331})SR^{333a1}$, $-O(C{=}O)OR^{2221}$, $-O(C{=}O)NR^{2221}R^{3331}$, $-O(C{=}O)SR^{2221}$, $-S(C{=}O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C{=}O)NR^{2221}R^{3331}$ substituents; or G^{11} is taken together with the carbon to which it is attached to form a double bond which is substituted with R^5 and G^{111};

R^2, R^{2a}, R^3, R^{3a}, R^{222}, R^{222}a, R^{333}, R^{333a}, R^{21}, R^{2a1}, R^{31}, R^{3a1}, R^{2221}, R^{222a1}, R^{3331}, and R^{333a1} are each independently equal to C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or in the case of $-NR^2R^3(R^{3a})_{j1}$ or $-NR^{222}R^{333}(R^{333}a)_{j1a}$ or $-NR^{222}R^{333}(R^{333}a)_{j2a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j3a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j6a,}$ R^2 and R^3 or R^{222} and R^{333}3 or R^{2221} and R^{3331} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted by one or more G^{111} substituents;

X^1 and Y^1 are each independently -O-, $-NR^7-$, $-S(O)_{j7}-$, $-CR^5R^6-$, $-N(C(O)OR^7)-$, $-N(C(O)R^7)-$, $-N(SO_2R^7)-$, $-CH_2O-$, $-CH_2S-$, $-CH_2N(R^7)-$, $-CH(NR^7)-$, $-CH_2N(C(O)R^7)-$, $-CH_2N(C(O)OR^7)-$, $-CH_2N(SO_2R^7)-$, $-CH(NHR^7)-$, $-CH(NHC(O)R^7)-$, $-CH(NHSO_2R^7)-$, $-CH(NHC(O)OR^7)-$, $-CH(OC(O)R^7)-$, $-CH(OC(O)NHR^7)-$, -CH=CH-, -C.ident.C-, $-C(=NOR^7)-$, -C(O)-, $-CH(OR^7)-$, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$ $-OC(O)N(R^7)-$, $-N(R^7)C(O)N(R^7)-$, $-NR^7C(O)O-$, $-S(O)N(R^7)-$, $-S(O)_2N(R^7)-$, $-N(C(O)R^7)S(O)-$, $-N(C(O)R^7)S(O)_2-$, $-N(R^7)S(O)N(R^7)-$, $-N(R^7)S(O)_2N(R^7)-$, $-C(O)N(R^7)C(O)-$, $-S(O)N(R^7)C(O)-$, $-S(O)_2N(R^7)C(O)-$, $-OS(O)N(R^7)-$, $-OS(O)_2N(R^7)-$, $-N(R^7)S(O)O-$, $-N(R^7)S(O)_2O-$, $-N(R^7)S(O)C(O)-$, $-N(R^7)S(O)_2C(O)-$, $-SON(C(O)R^7)-$, $-SO_2N(C(O)R^7)-$, $-N(R^7)SON(R^7)-$, $-N(R^7)SO_2N(R^7)-$, -C(O)O-, $-N(R^7)P(OR^8)O-$, $-N(R^7)P(OR^8)-$, $-N(R^7)P(O)(OR^8)O-$, $-N(R^7)P(O)(OR^8)-$, $-N(C(O)R^7)P(OR^8)O-$, $-N(C(O)R^7)P(OR^8)-$, -

N(C(O)R^7)P(O)(OR^8)O-, -N(C(O)R^7)P(OR^8)-, -CH(R^7)S(O)-, -CH(R^7)S(O)$_2$-, -CH(R^7)N(C(O)OR^7)-, -CH(R^7)N(C(O)R^7)-, -CH(R^7)N(SO_2R^7)-, -CH(R^7)O-, -CH(R^7)S-, -CH(R^7)N(R^7)-, -CH(R^7)N(C(O)R^7)-, -CH(R^7)N(C(O)OR^7)-, -CH(R^7)N(SO_2R^7)-, -CH(R^7)C(=NOR^7)-, -CH(R^7)C(O)-, -CH(R^7)CH(OR^7)-, -CH(R^7)C(O)N(R^7)-, -CH(R^7)N(R^7)C(O)-, -CH(R^7)N(R^7)S(O)-, -CH(R^7)N(R^7)S(O)$_2$-, -CH(R^7)OC(O)N(R^7)-, -CH(R^7)N(R^7)C(O)N(R^7)-, -CH(R^7)NR^7C(O)O-, -CH(R^7)S(O)N(R^7)-, -CH(R^7)S(O)$_2$N(R^7)-, -CH(R^7)N(C(O)R^7)S(O)-, -CH(R^7)N(C(O)R^7)S(O)-, -CH(R^7)N(R^7)S(O)N(R^7)-, -CH(R^7)N(R^7)S(O)$_2$N(R^7)-, -CH(R^7)C(O)N(R^7)C(O)-, -CH(R^7)S(O)N(R^7)C(O)-, -CH(R^7)S(O)$_2$N(R^7)C(O)-, -CH(R^7)OS(O)N(R^7)-, -CH(R^7)OS(O)$_2$N(R^7)-, -CH(R^7)N(R^7)S(O)O-, -CH(R^7)N(R^7)S(O)$_2$O-, -CH(R^7)N(R^7)S(O)C(O)-, -CH(R^7)N(R^7)S(O)$_2$C(O)-, -CH(R^7)SON(C(O)R^7)-, -CH(R^7)SO_2N(C(O)R^7)-, -CH(R^7)N(R^7)SON(R^7)-, -CH(R^7)N(R^7)SO_2N(R^7)-, -CH(R^7)C(O)O-, -CH(R^7)N(R^7)P(OR^8)O-, -CH(R^7)N(R^7)P(OR^8)-, -CH(R^7)N(R^7)P(O)(OR^8)O-, -CH(R^7)N(R^7)P(O)(OR^8)-, -CH(R^7)N(C(O)R^7)P(OR^8)O-, -CH(R^7)N(C(O)R^7)P(OR^8)-, -CH(R^7)N(C(O)R^7)P(O)(OR^8)O-, or -CH(R^7)N(C(O)R^7)P(OR^8)-;

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



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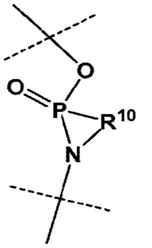

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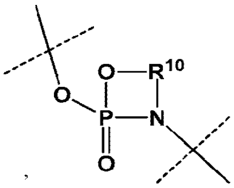

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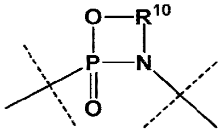

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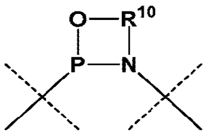

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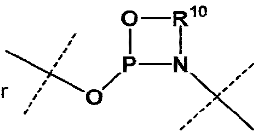


;

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

R^5, R^6, and G^{111} are each independently a C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}R^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R^{69}; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R^{69};

R^7 and R^8 are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G^{111} substituents;

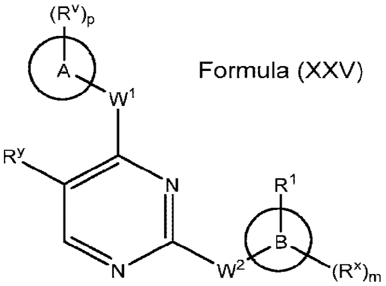
R^4 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G^{41} substituents;

R^{69} is equal to halo, $-OR^{78}$, -SH, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-CONR^{78}R^{88}$, $-NO_2$, -CN, $-S(O)_{j8}R^{78}$, $-SO_2NR^{78}R^{88}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or -N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$ $SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

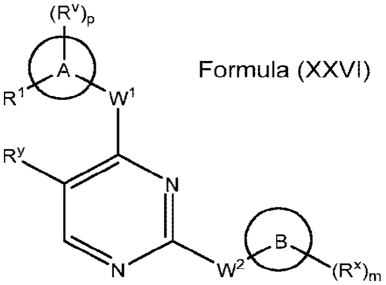
R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl,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

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

[00235] In an exemplary embodiment, the BTK inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 8,450,335 and 8,609,679, and U.S. Patent Application Publication Nos. 2010/0029610 A1, 2012/0077832 A1, 2013/0065879 A1, 2013/0072469 A1, and 2013/0165462 A1, the disclosures of which are incorporated by reference herein. In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI):



Formula (XXV)



Formula (XXVI)

or a pharmaceutically acceptable salt thereof, wherein:

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

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

R^1 is a warhead group;

R^y is hydrogen, halogen, —CN, —CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —C(O)N$(R)_2$;

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

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by —NR^2—, —N(R^2)C(O)—, —C(O)N(R^2)—, —N(R^2)SO_2—, —SO_2N(R^2)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

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

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

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

m and p are independently 0-4; and

R^x and R^v are independently selected from —R, halogen, —OR, —O$(CH_2)_q$OR, —CN, —NO_2, —SO_2R, —SO_2N$(R)_2$, —SOR, —C(O)R, —CO_2R, —C(O)N$(R)_2$, —NRC(O)R, —NRC(O)NR_2, —$NRSO_2$R, or —N$(R)_2$, wherein q is 1-4; or:

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

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

[00236] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI), wherein:

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

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

R^1 is -L-Y, wherein:

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, —SO_2N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR)—, —N=N—, or —C(=N_2)—;

Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -Q-Z, oxo, NO_2, halogen, CN, or C_{1-6} aliphatic, wherein:

Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —S—, —O—, —C(O)—, —SO—, or —SO_2—; and

Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN;

R^y is hydrogen, halogen, —CN, —CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —C(O)N$(R)_2$;

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

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by —NR^2—, —N(R^2)C(O)—, —C(O)N(R^2)—, —N(R^2)SO_2—, —SO_2N(R^2)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

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

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

R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^v are independently selected from —R, halogen, —OR, —O(CH$_2$)$_q$OR, —CN, —NO$_2$, —SO$_2$R, —SO$_2$N(R)$_2$, —SOR, —C(O)R, —CO$_2$R, —C(O)N(R)$_2$, —NRC(O)R, —NRC(O)NR$_2$, —NRSO$_2$R, or —N(R)$_2$, or:

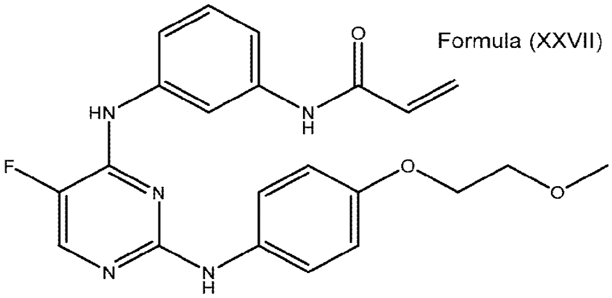
R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and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

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

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

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

[00237] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVII):


Formula (XXVII)

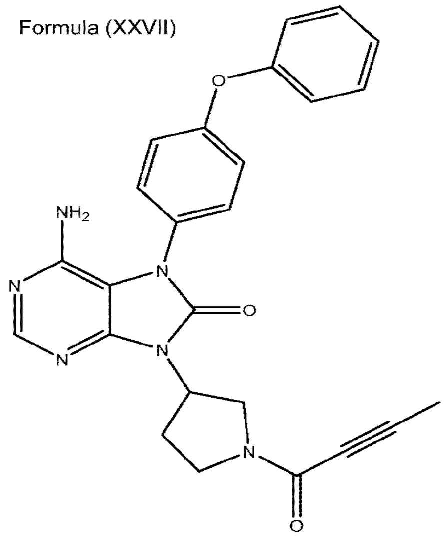
or a pharmaceutically acceptable salt thereof, or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of the besylate salt of this compound is described in U.S. Patent Application Publication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

[00238] In an exemplary embodiment, the BTK inhibitor is *N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00239] In an exemplary embodiment, the BTK inhibitor is (N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide), or a pharmaceutically acceptable salt thereof, or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of its besylate salt is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00240] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVIII):

Formula (XXVII)



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

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

[00241] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00242] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4- phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00243] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-[(3S)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4- phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00244] BTK inhibitors suitable for use in the described combination with a PI3K inhibitor, a PI3K-γ inhibitor, and/or a PI3K-δ inhibitor also include, but are not limited to, those described in, for example, International Patent Application Publication Nos. WO 2013/010868; WO 2012/158843; WO 2012/135944; WO 2012/135937; U.S. Patent Application Publication No. 2011/0177011; and U.S. Patent Nos. 8,501,751; 8,476,284; 8,008,309; 7,960,396; 7,825,118; 7,732,454; 7,514,444; 7,459,554; 7,405,295; and 7,393,848, the disclosures of each of which are incorporated herein by reference.

Pharmaceutical Compositions

[00245] In selected embodiments, the invention provides pharmaceutical compositions for treating solid tumor cancers, lymphomas and leukemia.

[00246] In selected embodiments, the invention provides pharmaceutical compositions of a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, and a BTK inhibitor for the treatment of disorders such as hyperproliferative disorder including but not limited to cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (*e.g.*, lymphoma and Kaposi's sarcoma) or viral-induced cancer. In some embodiments, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate (*e.g.*, benign prostatic hypertrophy (BPH)).

[00247] The invention further provides a composition for the prevention of blastocyte implantation in a mammal.

[00248] The invention also relates to a composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which can manifest as tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy,

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

[00249] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, and BTK inhibitor as the active ingredients, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[00250] The pharmaceutical compositions are administered as a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, and a BTK inhibitor. Where desired, other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations for use in combination separately or at the same time.

[00251] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v.

[00252] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 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.

[00253] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors of the invention is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v. v/v.

[00254] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors of the invention is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[00255] In selected embodiments, the amount of each of the PI3K and BTK inhibitors of the invention is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g.

[00256] In selected embodiments, the amount of each of the PI3K and BTK inhibitors of the invention is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g or 10 g.

[00257] Each of the PI3K and BTK inhibitors according to the invention is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently range from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[00258] Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing the indicated diseases or disorders can be tested using various animal models known in the art. Efficacy in treating, preventing and/or managing asthma can be assessed using the ova induced asthma model described, for example, in Lee *et al.*, J. Allergy Clin. Immunol. 118(2):403-9 (2006). Efficacy in treating, preventing and/or managing arthritis (*e.g.*, rheumatoid or psoriatic arthritis) can be assessed using the autoimmune animal models described in, for example, Williams *et al.*, Chem Biol, 17(2):123-34 (2010), WO 2009/088986, WO 2009/088880, and WO 2011/008302. Efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immuno-deficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke *et al.*, Clinics in Dermatology, 25: 596-605 (2007). Efficacy in treating, preventing and/or managing fibrosis or fibrotic conditions can be assessed using the unilateral ureteral obstruction model of renal fibrosis, which is described, for example, in Chevalier *et al.*, Kidney International 75:1145-1152 (2009); the bleomycin induced model of pulmonary fibrosis described in, for example, Moore *et al.*, Am. J. Physiol. Lung. Cell. Mol. Physiol. 294:L152-L160 (2008); a variety of liver/biliary fibrosis models described in, for example, Chuang *et al.*, Clin. Liver Dis.12:333-347 (2008) and Omenetti *et al.*, Laboratory Investigation 87:499-514 (2007) (biliary duct-ligated model); or any of a number of myelofibrosis mouse models such as described in Varicchio *et al.*, Expert Rev. Hematol. 2(3):315-334 (2009). Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto *et al.*, J. Invest. Dermatol. 112: 456-462 (1999). Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi *et al.*, Arthritis & Rheumatism, 60(10): 3118-3127 (2009). Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi *et al.*, Lupus, 19: 1029-1035 (2009); Ohl *et al.*, Journal of Biomedicine and Biotechnology, Article ID 432595 (2011); Xia *et al.*, Rheumatology, 50:2187-2196 (2011); Pau *et al.*, PLoS ONE, 7(5):e36761 (2012); Mustafa *et al.*, Toxicology, 290:156-168 (2011); Ichikawa *et al.*, Arthritis and Rheumatism, 62(2): 493-503 (2012); Ouyang *et al.*, J. Mol. Med. (2012); Rankin *et al.*, Journal of Immunology,188:1656-1667 (2012). Efficacy in treating, preventing and/or managing Sjogren's syndrome can be assessed using various mouse models described, for example, in Chiorini *et al.*, J. Autoimmunity, 33: 190-196 (2009).

[00259] To explore the role of PI3K signaling in diffuse large B-cell lymphoma (“DLBCL”), several DLBCL cell lines of varying molecular profiles may be utilized. In an exemplary embodiment, a cellular growth inhibition assay used five cell lines, including four GCB (SU-DHL-4, SU-DHL-6, OCI-LY-8 and WSU-DLCL-2) and one ABC (Ri-1) subtype. In an exemplary embodiment, a cellular growth inhibition assay used five cell lines that were OCI-LY-3, OCI-LY-7, Pfeiffer, Toledo and U2932. In an exemplary embodiment, evidence of PI3K pathway inhibition is measured by reduction in phospho (p)-AKT. In an exemplary embodiment, the kinetics of pathway modulation was characterized by examination of phosphorylation of AKT, PRAS40 and S6 following a time-course of treatment by a PI3Kinhibitor in selected cell lines. In one embodiment, upon B-cell receptor stimulation via antibody-induced crosslinking, some cell lines exhibited enhanced AKT phosphorylation.

[00260] In an exemplary embodiment, the combination effect of a PI3K inhibitor with a BTK inhibitor was observed in a cellular growth inhibition assay in the SU-DHL-4 cell line and in the OCI-LY-8 cell line with BCR crosslinking.

[00261] In one embodiment, provided herein is a method of treating, preventing and/or managing asthma. As used herein, "asthma" encompasses airway constriction regardless of the cause. Common triggers of asthma include, but are not limited to, exposure to an environmental stimulants (e.g., allergens), cold air, warm air, perfume, moist air, exercise or exertion, and emotional stress. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with asthma. Examples of the symptoms include, but are not limited to, severe coughing, airway constriction and mucus production.

[00262] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Oral Administration

[00263] In selected embodiments, the invention provides a pharmaceutical composition for oral administration containing the combination of a PI3K and BTK inhibitor, and a pharmaceutical excipient suitable for oral administration.

[00264] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of each of a PI3K and BTK inhibitor in combination and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of a fourth compound.

[00265] In selected embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00266] The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (*e.g.*, 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00267] Each of the PI3K and BTK inhibitors active ingredients can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00268] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00269] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00270] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[00271] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00272] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00273] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00274] Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00275] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00276] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00277] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00278] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00279] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00280] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00281] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00282] In an exemplary embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use - *e.g.*, compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00283] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, Ɛ-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, .epsilon.-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00284] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00285] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00286] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00287] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00288] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

[00289] In selected embodiments, the invention provides a pharmaceutical composition for injection containing the combination of the PI3K and BTK inhibitors and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00290] The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00291] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

[00292] Sterile injectable solutions are prepared by incorporating the combination of the PI3K and BTK inhibitors in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical Compositions for Topical Delivery

[00293] In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the combination of the PI3K and BTK inhibitors and a pharmaceutical excipient suitable for transdermal delivery.

[00294] Compositions of the present invention can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

[00295] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*, menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00296] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the combination of the PI3K and BTK inhibitors in controlled amounts, either with or without another agent.

[00297] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, *e.g.*, U.S. Patent Nos. 5,023,252; 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Pharmaceutical Compositions for Inhalation

[00298] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Other Pharmaceutical Compositions

[00299] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

[00300] Administration of the combination of the PI3K and BTK inhibitors or pharmaceutical composition of these compounds can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (*e.g.*, transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

[00301] The compositions of the invention may also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration may, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds of the invention may slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound of the invention may be administered, for example, by local delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound of the invention is admixed with a matrix. Such a matrix may be a polymeric matrix, and may serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for example, lactone-based polyesters or copolyesters such as polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly(ether-ester) copolymers (e.g. PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (*e.g.*, polyhydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices may be nondegrading or may degrade with time, releasing the compound or compounds. The combination of the PI3K and BTK inhibitors may be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds may be applied in a solvent and the solvent may be allowed to evaporate, thus forming a layer of compound onto the stent. Alternatively, the compound may be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the compound diffuses out of the body of the stent to contact the arterial wall. Such stents may be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound of the invention in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent may be removed via an additional brief solvent wash. In yet other embodiments, compounds of the invention may be covalently linked to a stent or graft. A covalent linker may be used which degrades *in vivo*, leading to the release of the compound of the invention. Any bio-labile linkage may be used for such a purpose, such as ester, amide or anhydride linkages. The combination of the PI3K and BTK inhibitors may additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the combination of the PI3K and BTK inhibitors via the pericard or via adventitial application of formulations of the invention may also be performed to decrease restenosis.

[00302] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00303] The invention also provides kits. The kits include each of the PI3K and BTK inhibitors, either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. The kit may further contain another agent. In selected embodiments, the PI3K and BTK inhibitors and the agent are provided as separate compositions in separate containers within the kit. In selected embodiments, the PI3K and BTK inhibitors and the agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer.

Dosages and Dosing Regimens

[00304] The amounts of the combination of the PI3K and BTK inhibitors administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

[00305] In selected embodiments, the combination of the PI3K and BTK inhibitors is administered in a single dose. Typically, such administration will be by injection - *e.g.*, intravenous injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of the combination of the PI3K and BTK inhibitors may also be used for treatment of an acute condition.

[00306] In selected embodiments, the combination of the PI3K and BTK inhibitors is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In other embodiments, the combination of the PI3K and BTK inhibitors is administered about once per day to about 6 times per day. In another embodiment the administration of the combination of the PI3K and BTK inhibitors continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00307] Administration of the agents of the invention may continue as long as necessary. In selected embodiments, the combination of the PI3K and BTK inhibitors is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the combination of the PI3K and BTK inhibitors is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In selected embodiments, the combination of the PI3K and BTK inhibitors is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects.

[00308] An effective amount of the combination of the PI3K and BTK inhibitors may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Methods of Treatment

[00309] In selected embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) and BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both the PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or the BTK inhibitor. In selected embodiments, the method relates to the treatment of cancer such as non-Hodgkin's lymphomas (such as diffuse large B-cell lymphoma), acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, bone (*e.g.*, metastatic bone), esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (e.g. lymphoma and Kaposi's sarcoma), viral-induced cancers, B cell acute lymphoblastic leukemia, Burkitt's leukemia, juvenile myelomonocytic leukemia, hairy cell leukemia, Hogkin's disease, multiple myeloma, mast cell leukemia, or mastocytosis. In selected embodiments, the method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate conditions (*e.g.*, benign prostatic hypertrophy (BPH)).

[00310] In selected embodiments, the invention relates to a method of treating an inflammatory, immune, or autoimmune disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) and BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both the PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or the BTK inhibitor. In selected embodiments, the invention also relates to a method of treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma and melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcets disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spoldylitis, Crohn's Disease, lupus, and lupus nephritis.

[00311] In selected embodiments, the invention relates to a method of treating a solid tumor cancer with a composition including a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, and a BTK inhibitor, wherein the dose is effective to inhibit signaling between the solid tumor cells and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts. In selected embodiments, the invention relates to a method of treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor and a PI3K inhibitor, wherein the dose is effective to inhibit signaling between the solid tumor cells and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts. Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing the indicated diseases or disorders can be tested using various models known in the art. For example, models for determining efficacy of treatments for pancreatic cancer are described in Herreros-Villanueva, et al. *World J. Gastroenterol.* **2012,** *18,* 1286-1294. Models for determining efficacy of treatments for breast cancer are described e.g. in A. Fantozzi, *Breast Cancer Res.* **2006,** *8,* 212. Models for determining efficacy of treatments for ovarian cancer are described e.g. in Mullany et al., *Endocrinology* **2012,** *153,* 1585-92; and Fong et al., *J. Ovarian Res.* **2009,** *2,* 12. Models for determining efficacy of treatments for melanoma are described e.g. in Damsky et al., *Pigment Cell & Melanoma Res.* **2010,** *23,* 853–859. Models for determining efficacy of treatments for lung cancer are described e.g. in Meuwissen et al., *Genes & Development,* **2005,** *19,* 643-664. Models for determining efficacy of treatments for lung cancer are described e.g. in Kim, *Clin. Exp. Otorhinolaryngol.* **2009,** *2,* 55-60; and Sano, *Head Neck Oncol.* **2009,** *1,* 32. Models for determining efficacy of treatments for colorectal cancer, including the CT26 model, are described below in the examples.

[00312] Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing other indicated diseases or disorders described here can also be tested using various models known in the art. Efficacy in treating, preventing and/or managing asthma can be assessed using the ova induced asthma model described, for example, in Lee et al., *J. Allergy Clin. Immunol.* **2006,** *118,* 403-9. Efficacy in treating, preventing and/or managing arthritis (*e.g.*, rheumatoid or psoriatic arthritis) can be assessed using the autoimmune animal models described in, for example, Williams et al., *Chem. Biol.* **2010,** *17,* 123-34, WO 2009/088986, WO 2009/088880, and WO 2011/008302. Efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immuno-deficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke et al., *Clinics in Dermatology*, **2007,** *25,* 596-605. Efficacy in treating, preventing and/or managing fibrosis or fibrotic conditions can be assessed using the unilateral ureteral obstruction model of renal fibrosis, which is described, for example, in Chevalier et al., *Kidney International* **2009,** *75,* 1145-1152; the bleomycin induced model of pulmonary fibrosis described in, for example, Moore et al., *Am. J. Physiol. Lung. Cell. Mol. Physiol.* **2008,** *294,* L152-L160; a variety of liver/biliary fibrosis models described in, for example, Chuang et al., *Clin. Liver Dis.* **2008,** *12,* 333-347 and Omenetti et al., *Laboratory Investigation*, **2007,** *87,* 499-514 (biliary duct-ligated model); or any of a number of myelofibrosis mouse models such as described in Varicchio et al., *Expert Rev. Hematol.* **2009,** *2,* 315-334. Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto et al., *J. Invest. Dermatol.* **1999,** *112,* 456-462. Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi et al., *Arthritis & Rheumatism,* **2009,** *60(10),* 3118-3127. Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi et al., *Lupus*, **2009,** *19,* 1029-1035; Ohl et al., *J. Biomed. & Biotechnol.*, Article ID 432595 (2011); Xia et al., *Rheumatology*, **2011,** *50,* 2187-2196; Pau et al., *PLoS ONE,* **2012,** *7(5)*, e36761; Mustafa et al., *Toxicology*, **2011,** *90,* 156-168; Ichikawa et al., *Arthritis & Rheumatism*, **2012,** *62(2)*, 493-503; Rankin et al., *J. Immunology,* **2012,** *188,* 1656-1667.

Efficacy in treating, preventing and/or managing Sjögren's syndrome can be assessed using various mouse models described, for example, in Chiorini et al., *J. Autoimmunity*, **2009,** *33,* 190-196.

EXAMPLES

[00313] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

Example 1 – Synergistic Combination of a BTK inhibitor and a PI3K-δ inhibitor

[00314] Ficoll purified mantle cell lymphoma (MCL) cells (2×10^5) isolated from bone marrow or peripheral blood were treated with each drug alone and with six equimolar concentrations of a BTK inhibitor (Formula XVIII) and a PI3K-δ inhibitor (Formula IX) ranging from 0.01 nM to 10 μM on 96-well plates in triplicate. Plated cells were then cultured in HS-5 conditioned media at 37°C with 5% CO_2. After 72 hours of culture, cell viability was determined using an (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The potential synergy of the combination of the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX at a given equimolar concentration was determined using the median effect model as described in Chou and Talalay, *Adv Enzyme Regul.* **1984,** *22,* 27-55. The statistical modeling was run in R using a script that utilizes the median effect model as described in Lee et al., *J. Biopharm. Stat.* **2007,** *17,* 461-80. A value of 1, less than 1, and greater than 1 using R defines an additive interaction, synergistic and antagonistic, respectively. The Lee et al. method calculates a 95% confidence interval for each data point. For each viability curve, to be considered synergistic, a data point must have an interaction index below 1 and the upper confidence interval must also be below 1. In order to summarize and demonstrate collective synergy results, an interaction dot blot was generated for the primary patient samples.

[00315] A similar approach was utilized to study diffuse large B cell lymphoma (DLBCL) (TMD8) and MCL (MINO) cell lines. Cells were treated with each drug alone and with six equimolar concentrations of the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX ranging from 0.003 nM to 1.0 μM (for TMD8) or 0.03 nM to 10 μM (for MINO) on 96-well plates in triplicate. Plated cells were then cultured in standard conditioned media plus FBS at 37°C with 5% CO_2. After 72 hours of culture, viability was determined using an MTS assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The results of the experiments described in this example are shown in FIG. 1, FIG. 2, FIG. 3, and FIG. 4.

Example 2 – Synergistic Combination of a BTK inhibitor and a PI3K-δ inhibitor

[00316] Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the Chou/Talalay method/algorithm by defining combination indexes for drug combinations. Information about experimental design for evaluation of synergy is described in e.g. Chou and Talalay, *Adv. Enzyme Regul.* **1984,** *22,* 27-55 and more generally in e.g. Greco et al., *Pharmacol. Rev.* **1995,** *47,* 331-385. The study was perfomred using the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX). Single agent activities were first determined in the various cell lines and subsequently, the combination indexes were established using equimolar ratios taking the single agent drug EC50s into consideration. For individual agents that displayed no single agent activity, equimolar ratios were used at fixed concentrations to establish combination indexes. The readout from 72 hour proliferation assays using Cell TiterGlo (ATP content of remaining cells) determined the fraction of cells that were effected as compared to untreated cells (Fa = fraction affected = (1- ((cells + inhibitor) – background signal) / ((cells + DMSO) – background signal)).

[00317] The combination index obtained was ranked according to Table 1.

TABLE 1. Combination Index (CI) Ranking Scheme

Range of CI	Description
<0.1	Very strong synergism
0.1-0.3	Strong synergism
0.3-0.7	Synergism
0.7-0.85	Moderate synergism
0.85-0.9	Slight synergism
0.9-1.1	Nearly additive
1.1-1.2	Slight antagonism
1.2-1.45	Moderate antagonism
1.45-3.3	Antagonism
3.3-10	Strong antagonism
>10	Very strong antagonism

[**00318**] The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are given in FIG. 5 to FIG. 37. The results of the cell line studies are summarized in Table 2.

TABLE 2. Summary of results of the combination of a BTK inhibitor with a PI3K-δ inhibitor (S = synergistic, A = additive, X = no effect).

Cell Line	Indication	ED25	ED50	ED75	ED90
Raji	Burkitt's	S	S	S	S
Ramos	Burkitt's	X	X	X	X
Daudi	Burkitt's	S	S	S	S
Mino	MCL	S	S	S	S
Pfeiffer	iNHL	S	S	S	S
DOHH	iNHL	S	S	S	S
REC-1	iNHL	S	S	A	A
U937	Myeloid	S	S	S	S
K562	CML	X	X	X	X
SU-DHL-1	ABC	S	A	X	X
SU-DHL-2	ABC	S	S	S	S
HBL-1	ABC	S	S	S	S
TMD8	ABC	S	S	S	S
LY19	GCB	X	X	X	X
LY7	GCB	S	S	S	S
LY1	GCB	X	X	X	X
SU-DHL-6	GCB	S	S	S	S
SupB15	B-ALL	S	S	S	S
CCRF	B-ALL	S	A/S	X	X

Example 3 – BTK Inhibitory Effects on a Solid Tumor Microenvironment in a Orthotopic Pancreatic Cancer Model

[00319] An orthotopic pancreatic cancer model was used to investigate the therapeutic efficacy of the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) through treatment of the solid tumor microenvironment. Mice were dosed orally with 15 mg/kg of Formula (XVIII), 15 mg/kg of Formula (IX), or a combination of 15 mg/kg of both drugs.

[00320] Cell line derived from KrasG12D;Trp53R172H;Pdx1-Cre (KPC) mice were orthotopically implantated into the head of the pancreas after 35 passages. Based on the mice background from where the cell lines were generated, 1×10^6 cells were injected in C57BL/6 mice. Throughout the experiment, animals were provided with food and water ad libitum and subjected to a 12-h dark/light cycle. Animal studies were performed in accordance with the U.S. Public Health Service "Guidelines for the Care and Use of Laboratory Animals" (IACUC). After euthanization, pancreatic tumors were dissected out, weighed and single cell suspensions were prepared for flow cytometry analysis.

[00321] Results of the experiments are shown in FIG. 38, which illustrates tumor growth suppression in the orthotopic pancreatic cancer model. The statistical p-value (presumption against null hypothesis) is shown for each tested single agent and for the combination against the vehicle. The results show that all three treatments provide statistically significant reductions in tumor volume in the pancreatic cancer model.

[00322] Additional results of the experiments relating to treatment of the tumor microenvironment are shown in FIG. 39 to FIG. 41. FIG. 39 shows the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both drugs on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice. FIG. 40 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice. FIG. 41 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice. The results shown in FIG. 39 to FIG. 41 demonstrate that of the BTK inhibitor of Formula (XVIII) and the combination of the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) reduce immunosuppressive tumor associated myeloid cells and Tregs in pancreatic tumor-bearing mice. Overall, BTK inhibition with Formula (XVIII) or a combination of Formula (XVIII) and Formula (IX) significantly reduced tumor burden in an aggressive orthotopic PDA model, decreased immature myeloid infiltrate, reduced the number of tumor associated macrophages, and reduced the number of immunospressive Tregs, demonstrating a strong effect on the tumor microenvironment.

CLAIMS

We claim:

1. A method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor and a Bruton's tyrosine kinase (BTK) inhibitor.

2. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K-γ inhibitor.

3. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K-δ inhibitor.

4. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K-γ,δ inhibitor.

5. The method of paragraph 1, wherein the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers.

6. The method of paragraph 1, wherein the combination of the PI3K inhibitor with the BTK inhibitor is administered by intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

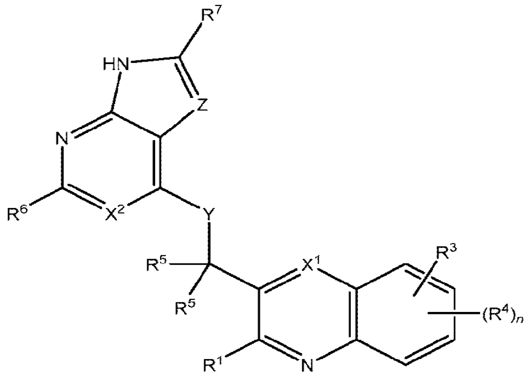
7. The method of paragraph 1, wherein the PI3K inhibitor or BTK inhibitor is in the form of a pharmaceutically acceptable salt.

8. The method of paragraph 1, wherein the PI3K inhibitor is administered to the subject before administration of the BTK inhibitor.

9. The method of paragraph 1, wherein the PI3K inhibitor is administered concurrently with the administration of the BTK inhibitor.

10. The method of paragraph 1, wherein the PI3K inhibitor is administered to the subject after administration of the BTK inhibitor.

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



or any pharmaceutically-acceptable salt thereof, wherein:

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

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

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

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one 0 or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C$_{1\text{-}4}$alkyl, OC$_{1_4}$alkyl, OC$_{1\text{-}4}$haloalkyl, NHC$_{1\text{-}4}$, N(C$_{1\text{-}4}$alkyl)C$_{1\text{-}4}$alkyl and C$_{1\text{-}4}$haloalkyl;

R^2 is selected from halo, C$_{1\text{-}4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a. —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2\text{-}6}$alkylNR^{a}R^a, —OC$_{2\text{-}6}$alkylOR^a, —SR^a, OS(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}R^a, —NR^{a}C$_{2\text{-}6}$ alkylNR^{a}R^a and —NR^{a}C$_{2\text{-}6}$alkylOR^a; or R^2 is selected from C$_{1\text{-}6}$alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C$_{1\text{-}3}$alkyl)heteroaryl, —(C$_{1\text{-}3}$alkyl)heterocycle, —O(C$_{1\text{-}3}$alkyl)heteroaryl, —O(C$_{1\text{-}3}$alkyl)heterocycle, —NR^a(C$_{1\text{-}3}$alkyl)heteroaryl, —NR^a(C$_{1\text{-}3}$alkyl)heterocycle, —(C$_{1\text{-}3}$alkyl)phenyl, —O(C$_{1\text{-}3}$alkyl)phenyl and —NR^a(C$_{1-3}$alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C$_{1-4}$haloalkyl, OC$_{1-4}$alkyl, Br, Cl, F, I and C$_{1-4}$alkyl;

R^3 is selected from H, halo, C$_{1-4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)R^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^2, —OC$_{2-6}$alkylNR^{a}R^a, —OC$_{2-6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a, —NR^{a}R^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^{a}R^a, —N(R^a)C(=NR^a)NR^{a}R^a, —N(R^a)S(=O)$_2$R^a, —N(R^a)S(=O)$_2$NR^{a}NR^{a}R^a, —NR^{a}C$_{2-6}$alkylOR^a, C$_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C$_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C$_{1-6}$haloalkyl, OC$_{1-6}$alkyl, Br, Cl, F, I and C$_{1-6}$alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C$_{1-4}$alkyl, OC$_{1-4}$alkyl, OC$_{1-4}$haloalkyl, NHC$_{1-4}$alkyl, N(C$_{1-4}$alkyl)C$_{1-4}$alkyl or C$_{1-4}$haloalkyl;

R^5 is, independently, in each instance, H, halo, C$_{1-6}$alkyl, C$_{1-4}$haloalkyl, or C$_{1-6}$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC$_{1-4}$alkyl, C$_{1-4}$alkyl, C$_{1-3}$haloalkyl, OC$_{1-4}$alkyl, NH$_2$, NHC$_{1-4}$alkyl, N(C$_{1-4}$alkyl)C$_{1-4}$alkyl; or both R^5 groups together form a C$_{3-6}$spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC$_{1-4}$alkyl, C$_{1-4}$alkyl, C$_{1-3}$haloalkyl, OC$_{1-4}$alkyl, NH$_2$, NHC$_{1-4}$alkyl, N(C$_{1-4}$alkyl)C$_{1-4}$alkyl;

R^6 is selected from H, halo, C$_{1-6}$alkyl, C$_{1-4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a;

R^7 is selected from H, halo, C$_{1-6}$alkyl, C$_{1-4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^a, —C(=NR^a)NR^{a}R^a, —S(=O)R^a, —S(=O)$_2$R^a, —S(=O)$_2$NR^{a}R^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^{a}R^a;

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

R^9 is selected from H, halo, C$_{1-4}$haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^{a}R^{a}C(=NR^a)NR^{a}R^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^{a}R^a, —OC(=O)N(R^a)S(=O)$_2$R^a, —OC$_{2-6}$alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2$R^a, —

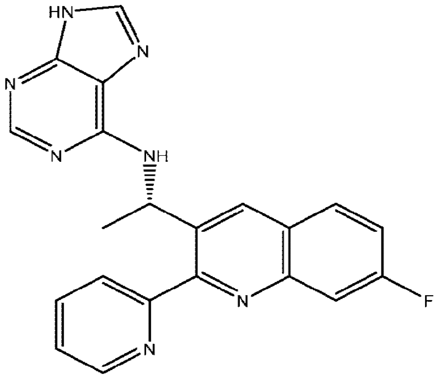
$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, NR^aR^a, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(O)NR^aR^aN(R^aC(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}$ alkylNR^aR^a, —NR^aC_{1-6}alkyl, phenyl, benzyl,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

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

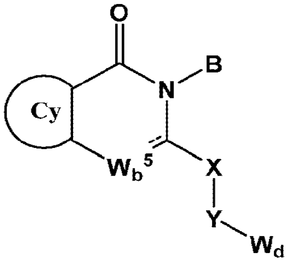
R^{11} is H or C_{1-4}alkyl;

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

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



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



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

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

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

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