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Description

[0001] Disclosed herein are compounds capable of selectively inhibiting one or more isoform(s) of class I PI3K without substantially affecting the activity of the remaining isoforms of the same class. For example, examples of inhibitors capable of selectively inhibiting PI3K-δ and/or PI3K-γ, but without substantially affecting the activity of PI3K-α and/or PI3K-β are disclosed. The inhibitors disclosed herein can be effective in ameliorating disease conditions associated with PI3K-δ and/or PI3K-γ activity. In one implementation, the compounds may be capable of selectively inhibiting PI3K-γ over PI3K-δ.

BACKGROUND

[0002] The activity of cells can be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases (Gaestel et al. Current Medicinal Chemistry (2007) 14:2214-2234).

[0003] Kinases represent a class of important signaling molecules. Kinases can generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities. Protein kinases are enzymes that phosphorylate other proteins and/or themselves *(i.e.,* autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (*e.g.*, erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (*e.g.*, mTorC1, mTorC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

[0004] Lipid kinases are enzymes that catalyze the phosphorylation of lipids. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. Certain lipid kinases are membrane associated and they catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include phosphoinositide(s) kinases (*e.g.*, PI3-kinases, PI4-kinases), diacylglycerol kinases, and sphingosine kinases.

[0005] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems inhuman cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K signaling is involved in many disease states including 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.

[0006] US 2013/029982 A1, US 2013/053362 A1, WO 2013/154878 A1 and EP 3119397 A1 each disclose families of heterocyclic compounds and pharmaceutical compositions that modulate kinase activity, including PI3 kinase activity, along with compounds, pharmaceutical compositions and methods of treatment of diseases and conditions associated with kinase activity, including PI3 kinase activity. WO 2013/012918 A1 discloses a group of compounds and pharmaceutical compositions suitable for use as PI3 kinase modulators, as well as their use in the treatment of diseases such as cancer. WO 2012/037204 A1 discloses a PI3K-delta inhibitor, along with pharmaceutically acceptable salts and solvates thereof, and methods of making and using those compounds.

[0007] PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidy linositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (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. The class II and III PI3Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PI3Ks are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

[0008] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K-δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K-δ is integrally 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 integral 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, and auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. Other class I PI3K involved in immune system function includes PI3K-γ, which plays a role in leukocyte signaling and has been implicated

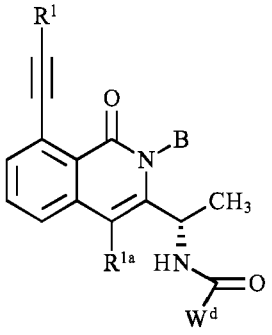
in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus. For example, PI3K-γ and PI3K-δ are highly expressed in leukocytes and have been associated with adaptive and innate immunity; thus, these PI3K isoforms can be important mediators in inflammatory disorders and hematologic malignancies.

[0009] The gamma (γ) isoform of class I PI3K consists of a catalytic subunit p110γ, which is associated with a p101 regulatory subunit. PI3K-γ is regulated by G protein-coupled receptors (GPCRs) via association with the β/γ subunits of heterotrimeric G proteins. PI3K-γ is expressed primarily in hematopoietic cells and cardiomyocytes and is involved in inflammation and mast cell function. Inhibitors of PI3K-γ are useful for treating a variety of inflammatory diseases, allergies, and cardiovascular diseases, among others.

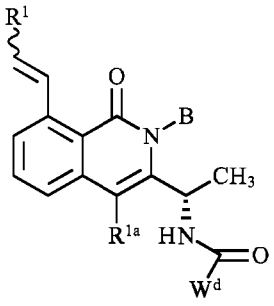
[0010] Unlike PI3K-δ, the beta (β) isoform of class I PI3K appears to be ubiquitously expressed. PI3K-β has been implicated primarily in various types of cancer including PTEN-negative cancer (Edgar et al. Cancer Research (2010) 70(3): 1164-1172), and HER2-overexpressing cancer such as breast cancer and ovarian cancer.

SUMMARY

[0011] In one aspect of the present invention there is provided a compound of Formula (I) or Formula (A):



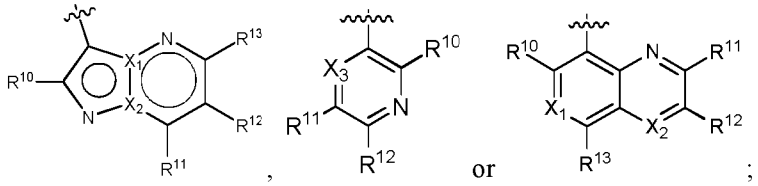
Formula (I) or



Formula (A),

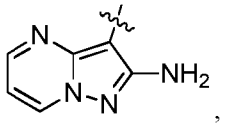
wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -COR^2, -$COOR^3$, or - $CONR^4R^5$;
B is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -COR^2, -$COOR^3$, - $CONR^4R^5$, or -$Si(R^6)_3$;
wherein R^2, R^3, R^4, R^5, and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;
W^d is

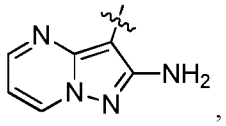


wherein
X_1, X_2 and X_3 are each independently C, CR^{13}, or N; and
R^{10}, R^{11}, R^{12}, and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR'R" wherein R' and R" together with the nitrogen to which they are attached form a cyclic moiety;
wherein R^{1a} is hydrogen, halo, alkyl, alkenyl, alkynyl, or CN;
wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
wherein each cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with one or more halo, alkyl,

alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, S(O)(alkyl), or $S(O)_2$(alkyl);
wherein in Formula (I), when R^{1a} is H, B is unsubstituted phenyl, and W^d is

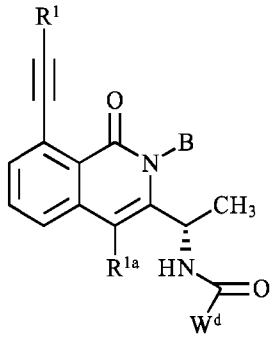


then R^1 is not hydrogen, methyl, $(CH_2)NH_2$, or $(CH_2)_2NH_2$; and
wherein in Formula (A), when R^{1a} is H, B is unsubstituted phenyl, and W^d is



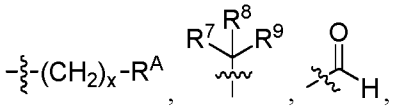
then R^1 is not phenyl;
or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable form thereof.

[0012] In some embodiments, the compound may be a compound of Formula (I):



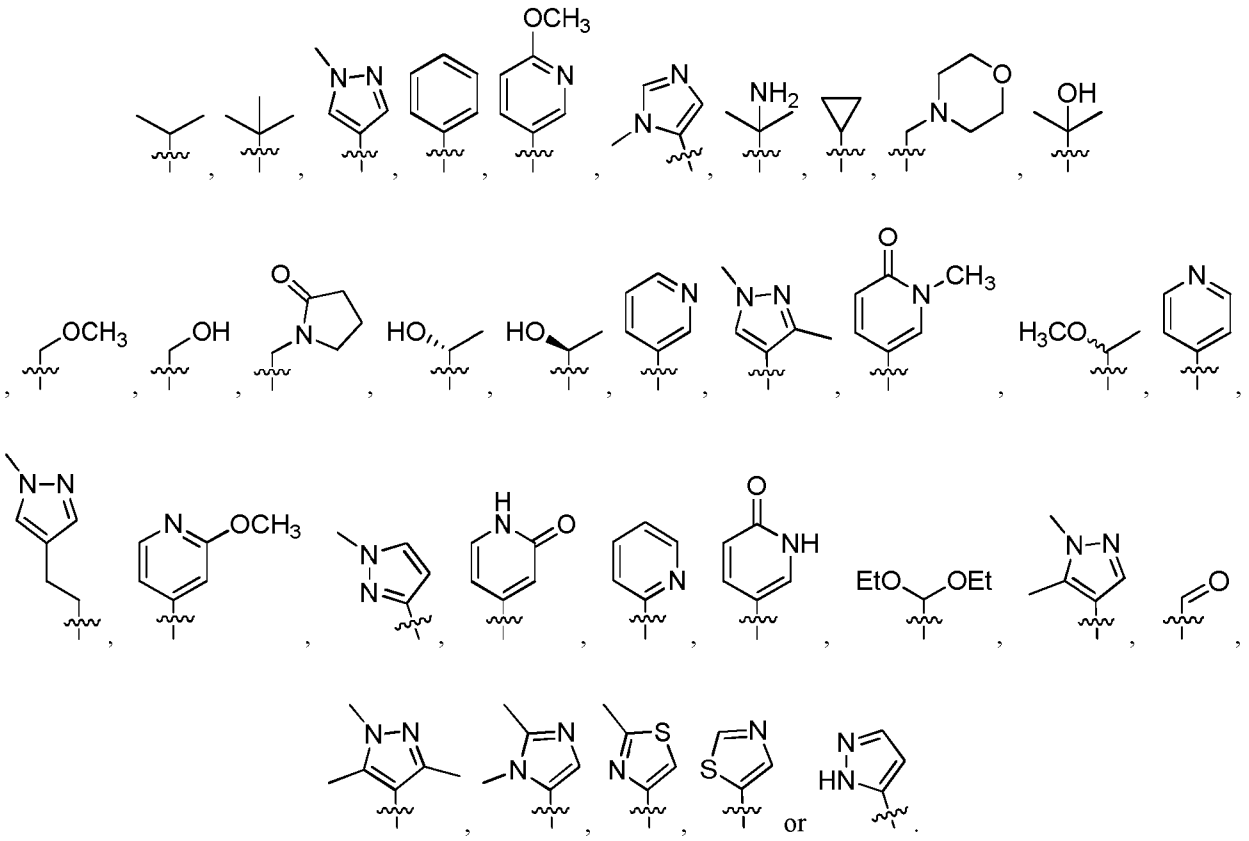
Formula (I).

[0013] Suitably, R^1 may be branched alkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, 5- or 6-membered cycloalkyl, or 5- to 6-membered heterocycloalkyl,



cyclopropyl or methyl;
wherein R^A is OH, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;
x is 1, 2, 3, 4, 5, or 6; and
R^7, R^8, and R^9 are each, independently, hydrogen, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

[0014] R^1 may be methyl,



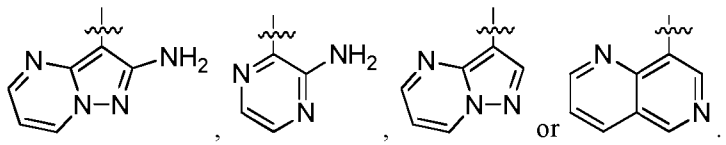
[0015] In some embodiments, R^1 may be a 5- to 10-membered heteroaryl, preferably a 6-membered heteroaryl, more preferably pyridinyl or pyrimidinyl; or a 5-membered heteroaryl, preferably thiazolyl, pyrazolyl or imidazolyl; wherein the heteroaryl is optionally substituted with one or more alkyl groups.

[0016] In some embodiments, B may be aryl, heteroaryl, cycloalkyl, preferably 3- to 6-membered cycloalkyl, more preferably

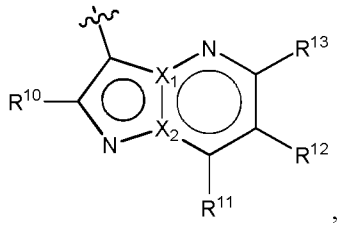
; or heterocycloalkyl.

[0017] Suitably, B may be unsubstituted phenyl or phenyl substituted with 1, 2, or 3 occurrence(s) of R^z; wherein each instance of W is independently halo or alkyl.

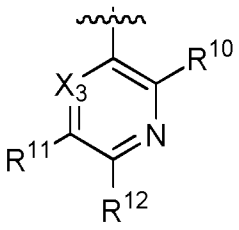
[0018] In some embodiments, W^d may be:



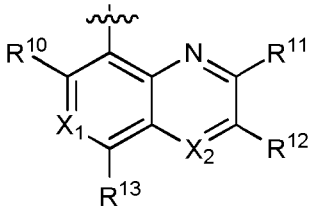
[0019] Suitably, W^d maybe:



wherein one of X_1 and X_2 is C and the other is N; or
W^d is



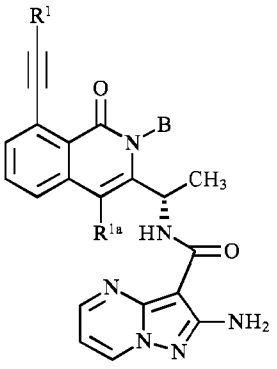
wherein X_3 is N or CR^{13}; or
W^d is



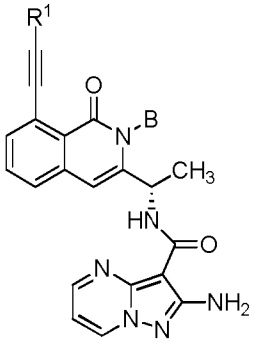
wherein one of X_1 and X_2 is N and the other is CR^{13}.

[0020] In some embodiments, R^{1a} may be H.

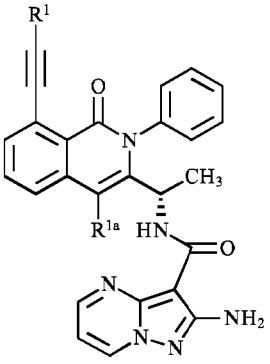
[0021] Suitably, the compound may be a compound of formula II, III, V, VI, VIII, IX or XII:



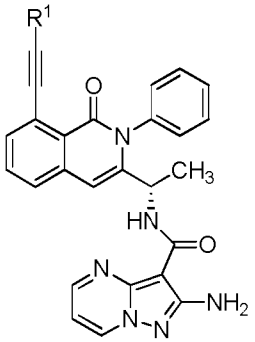
II,



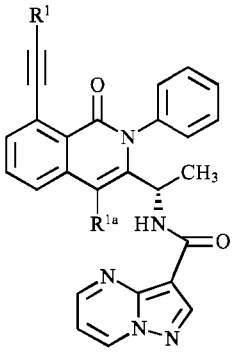
III,



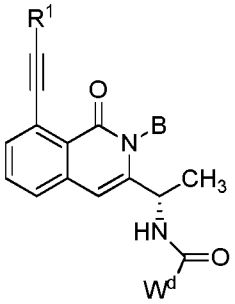
V,



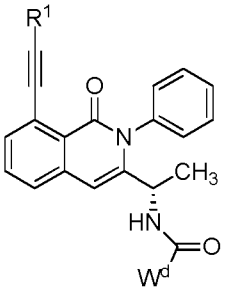
VI,



VIII,

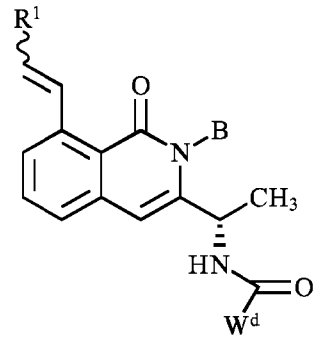


IX or



XII.

[0022] Alternatively, the compound may be a compound of Formula (A):

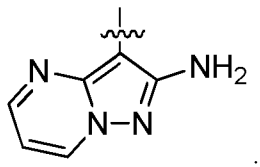


Formula (A)

and R^1 is alkyl or heteroaryl.

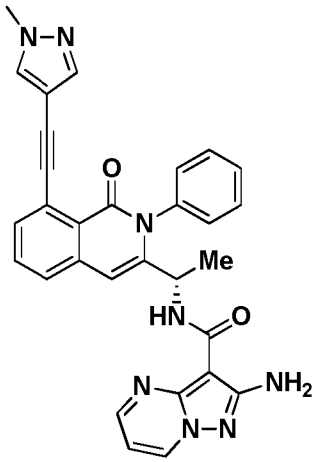
[0023] In some embodiments, the compound may be a compound of Formula (A) and B is phenyl.

[0024] In some embodiments, the compound may be a compound of Formula (A) and W^d is



[0025] The compound, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or pharmaceutically acceptable form thereof of claim 1; wherein the compound is in an (S)-stereochemical configuration, preferably having an enantiomeric purity greater than 75%.

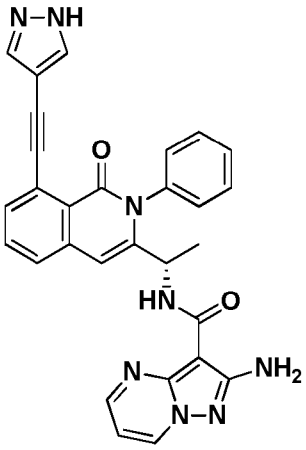
[0026] In some embodiments, the compound may be Compound 4 below:



Compound 4

or a pharmaceutically acceptable salt thereof.

[0027] Alternatively, the compound may be Compound 80 below:



Compound 80

or a pharmaceutically acceptable salt thereof.

[0028] In one embodiment, the compound of Formula (I) or (A) is predominately in an (S)-stereochemical configuration. In one embodiment, the compound of Formula (I) or (A) is the S enantiomer having an enantiomeric excess selected from greater than about 25%, greater than about 55%, greater than about 80%, greater than about 90%, and greater than about 95%.

[0029] In one embodiment, the compound is present in a pharmaceutical composition comprising the compound, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0030] In certain embodiments, a compound disclosed herein selectively modulates PI3K gamma isoform. In certain embodiments, the compound selectively inhibits the gamma isoform over the alpha or beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. In one embodiment, the selectivity of PI3K gamma isoform over PI3K alpha or beta isoform is measured by the ratio of the IC_{50} value against PI3K alpha or beta isoform to the IC_{50} value against PI3K gamma isoform.

[0031] In certain embodiments, a compound disclosed herein selectively modulates PI3K gamma isoform over the delta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. In one embodiment, the selectivity of PI3K gamma isoform over PI3K delta isoform is measured by the ratio of the IC_{50} value against PI3K delta isoform to the IC_{50} value against PI3K gamma isoform.

[0032] In certain embodiments, a compound as disclosed herein selectively modulates PI3K delta isoform. In certain embodiments, the compound selectively inhibits the delta isoform over the alpha or beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. In one embodiment, the selectivity of PI3K delta isoform over PI3K alpha or beta isoform is measured by the ratio of the IC_{50} value against PI3K alpha or beta isoform to the IC_{50} value against PI3K delta isoform.

[0033] In certain embodiments, provided herein is a composition (e.g., a pharmaceutical composition) comprising a compound described herein and a pharmaceutically acceptable excipient.

[0034] In another aspect of the present invention therefore, there is provided a pharmaceutical composition comprising a compound or pharmaceutically acceptable form thereof in accordance with the invention and a pharmaceutically acceptable excipient, diluent, or carrier.

[0035] In some embodiments, the pharmaceutical composition may further comprise a PI3K-delta inhibitor; preferably a PI3K-delta selective inhibitor, GS-1101 (Cal-101), or AMG319

[0036] The present disclosure also relates to a method for treating a disease or disorder described herein which comprises administering a therapeutically effective amount of a compound or a pharmaceutical composition according to the invention to a subject.

[0037] Accordingly, in another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating cancer; particularly a hematological cancer, more particularly leukemia or lymphoma, or acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL), Waldenstrom's macroglobulinemia (WM), peripheral T cell lymphomas (PTCL), adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGL), acute myelocytic leukemia (AML), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), mastocytosis, multiple myeloma (MM), myelodysplastic syndrome (MDS) or myeloproliferative disorder (MPD).

[0038] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating a solid tumor.

[0039] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating cancer; particularly a brain cancer, a skin cancer, head and neck cancer, or a neuroendocrine cancer; a pancreatic cancer, a lung cancer, a breast cancer, a prostate cancer, a testicular cancer, an esophageal cancer, a liver cancer, a gastric cancer, a colon cancer, a colorectal cancer, an ovarian cancer, a cervical cancer, a uterine cancer, an endometrial cancer, a bladder cancer, a kidney cancer or a viral-induced cancer.

[0040] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating cancer; particularly a medulloblastoma, a basal cell carcinoma, a glioma, a hepatocellular cancer, a gastrointestinal stromal tumor (GIST), a melanoma, a primitive neuroectodermal tumor (PNT), a soft tissue sarcoma, fibrosarcoma, myxosarcoma,

liposarcoma, a chondrosarcoma, an osteosarcoma, a chordoma, an angiosarcoma, an endotheliosarcoma, a lymphangiosarcoma, a lymphangioendotheliosarcoma, a synovioma, a mesothelioma, a leiomyosarcoma, a transitional cell carcinoma in urinary bladder, an epithelial carcinoma, a squamous cell carcinoma, an adenocarcinoma, a bronchogenic carcinoma, a renal cell carcinoma, a malignant hepatoma, a carcinoid tumor or glioblastoma.

[0041] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating a solid tumor, particularly melanoma, lung cancer, more particularly non-small cell lung cancer, head and neck cancer, more particularly head and neck squamous cell carcinoma, renal cell carcinoma, bladder cancer, breast cancer, colon cancer, glioblastoma, adrenal gland cancer, mesothelioma, colorectal cancer, ovarian cancer or endometrial cancer.

[0042] In some embodiments, the cancer may be metastatic.

[0043] In some embodiments, the cancer may be relapsed after, or refractory to, a prior therapy.

[0044] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating a bone disorder in accordance with the present invention, particularly a bone disorder that results disruption of a function of an osteoclast.

[0045] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating a respiratory disease; particularly a respiratory disease selected from asthma, cystic fibrosis, emphysema, chronic obstructive pulmonary disorder (COPD), chronic bronchitis, bronchiectasis, acute respiratory distress syndrome, respiratory tract diseases, pleural cavity diseases and pulmonary hypertension.

[0046] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention for use in treating an inflammatory disease or an auto-immune disease; particularly arthritis.

[0047] Suitably, the compound, pharmaceutically acceptable form or composition may be administered in the amount of about 0.1 mg to about 100 mg per day, about 1 mg to 50 mg per day, about 5 mg to 40 mg per day or about 10 mg to 30 mg per day.

[0048] Suitably, the compound, pharmaceutically acceptable form or composition may be administered every other day, once per day or twice per day.

[0049] In some embodiments, the compound, pharmaceutically acceptable form or composition may be for administration orally or by inhalation.

[0050] In yet another aspect of the present invention there is provided a compound or pharmaceutically acceptable form thereof or a pharmaceutical composition in accordance with the present invention, wherein the compound, pharmaceutically acceptable form or composition is for administration in combination with one or more second therapeutic agents; preferably Norvir (ritonavir); a PI3K-delta inhibitor, more preferably a PI3K-delta selective inhibitor, GS-1101 (Cal-101), or AMG319; or an mTOR inhibitor; or a costimulatory modulator, an immunostimulant or a CXCL12/CXCR4 inhibitor; a HDAC inhibitor, a proteasome inhibitor, a CD28 antibody, a CD30 antibody or a CD40 antibody; GM-CSF; or gemcitabine, cyclophosphamide, docetaxel, paclitaxel, 5-FU or temozolomide; or a second therapy; preferably a radiation therapy, the compound, pharmaceutically acceptable form thereof, or composition preferably being administered subsequent to, concurrently with or alone after discontinuing the radiation therapy.

[0051] Also disclosed herein is a method of making a compound described herein.

DETAILED DESCRIPTION

[0052] 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 specification pertains.

[0053] As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

[0054] As used herein, and unless otherwise indicated, the term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain contexts, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain contexts, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0055] As used herein, "agent" or "biologically active agent" or "second active agent" refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include simple or complex organic or inorganic molecules, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, an antibody fragment, a vitamin, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound, and metabolites thereof. Various compounds can be synthesized, for example, small molecules and oligomers (e.g., oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like. A skilled artisan can readily recognize that there is

no limit as to the structural nature of the agents of this disclosure.

[0056] The term "agonist" as used herein refers to a compound or agent having the ability to initiate or enhance a biological function of a target protein or polypeptide, such as increasing the activity or expression of the target protein or polypeptide. Accordingly, the term "agonist" is defined in the context of the biological role of the target protein or polypeptide. While some agonists herein specifically interact with (e.g., bind to) the target, compounds and/or agents that initiate or enhance a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

[0057] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound or agent having the ability to inhibit a biological function of a target protein or polypeptide, such as by inhibiting the activity or expression of the target protein or polypeptide. Accordingly, the terms "antagonist" and "inhibitor" are defined in the context of the biological role of the target protein or polypeptide. While some antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target protein or polypeptide are also specifically included within this definition. Non-limiting examples of biological activity inhibited by an antagonist include those associated with the development, growth, or spread of a tumor, or an undesired immune response as manifested in autoimmune disease.

[0058] An "anti-cancer agent", "anti-tumor agent" or "chemotherapeutic agent" refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents. "Chemotherapy" means the administration of one or more chemotherapeutic drugs and/or other agents to a cancer patient by various methods, including intravenous, oral, intramuscular, intraperitoneal, intravesical, subcutaneous, transdermal, or buccal administration, or inhalation, or in the form of a suppository.

[0059] The term "cell proliferation" refers to a phenomenon by which the cell number has changed as a result of division. This term also encompasses cell growth by which the cell morphology has changed (e.g., increased in size) consistent with a proliferative signal.

[0060] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to 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.

[0061] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or pharmaceutical composition described herein that is sufficient to effect the intended application including, but not limited to, disease treatment, as illustrated below. The therapeutically effective amount can vary depending upon the intended application *(in vitro* or *in vivo),* or the subject and disease condition being treated, *e.g.,* the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, 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.,* reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on, for example, the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0062] As used herein, the terms "treatment", "treating", "palliating" and "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including, but not limited to, therapeutic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder.

[0063] As used herein, the terms "prevention" and "preventing" are used herein to refer to an approach for obtaining beneficial or desired results including, but not limited, to prophylactic benefit. For prophylactic benefit, the pharmaceutical compositions can be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0064] 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.

[0065] " Signal transduction" is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response. A "modulator" of a signal transduction pathway refers to a compound which modulates the activity of one or more cellular proteins mapped to the same specific signal transduction pathway. A modulator can augment (agonist) or suppress (antagonist) the activity of a signaling molecule.

[0066] The term "selective inhibition" or "selectively inhibit" as applied to a biologically active agent refers to the agent's ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with the target. For example, a compound that selectively inhibits one isoform of PI3K over another isoform

of PI3K has an activity of at least greater than about IX against a first isoform relative to the compound's activity against the second isoform (e.g., at least about 2X, 3X, 5X, 10X, 20X, 50X, 100X, 200X, 500X, or 1000X). In certain embodiments, these terms refer to (1) a compound of described herein that selectively inhibits the gamma isoform over the alpha, beta, or delta isoform; or (2) a compound described herein that selectively inhibits the delta isoform over the alpha or beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 1, greater than a factor of about 2, greater than a factor of about 3, greater than a factor of about 5, greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, which in turn can be measured by, *e.g., in vitro* or *in vivo* assays such as those described in Examples described herein. In one embodiment, the selectivity of a first PI3K isoform over a second PI3K isoform is measured by the ratio of the IC_{50} value against the second PI3K isoform to the IC_{50} value against the first PI3K gamma isoform. For example, a delta/gamma selectivity ratio of a compound can be measured by the ratio of the compound's inhibitory activity against the delta isoform in terms of IC_{50} or the like to the compound's inhibitory activity against the gamma isoform in terms of IC_{50} or the like. If the delta/gamma selectivity ratio is larger than 1, the compound selectively inhibits the gamma isoform over the delta isoform. In certain embodiments, the PI3K gamma isoform IC_{50} activity of a compound of provided herein can be less than about 1000 nM, less than about 500 nM, less than about 400 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In certain embodiments, the PI3K delta isoform IC_{50} activity of a compound provided herein can be less than about 1000 nM, less than about 500 nM, less than about 400 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 75 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM.

[0067] "Radiation therapy" means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as, but not limited to, alpha-particle emitting radionuclides (e.g., actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (e.g., beta emitters), conversion electron emitters (e.g., strontium-89 and samarium-153-EDTMP), or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons.

[0068] "Subject" to which administration is contemplated includes, but is not limited to, humans (e.g., a male or female of any age group, *e.g.,* a pediatric subject *(e.g.,* infant, child, adolescent) or adult subject *(e.g.,* young adult, middle-aged adult or senior adult)) and/or other primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys.

[0069] The term *"in vivo"* refers to an event that takes place in a subject's body.

[0070] The term *"in vitro"* refers to an event that takes places outside of a subject's body. For example, an *in vitro* assay encompasses any assay conducted outside of a subject. *In vitro* assays encompass cell-based assays in which cells, alive or dead, are employed. *In vitro* assays also encompass a cell-free assay in which no intact cells are employed.

[0071] As used herein, "pharmaceutically acceptable esters" include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids, and boronic acids.

[0072] As used herein, "pharmaceutically acceptable enol ethers" include, but are not limited to, derivatives of formula -C=C(OR) where R can be selected from alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula -C=C(OC(O)R) where R can be selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl.

[0073] As used herein, a "pharmaceutically acceptable form" of a disclosed compound includes, but is not limited to, pharmaceutically acceptable salts, hydrates, solvates, isomers and isotopically labeled derivatives of disclosed compounds. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, isomers and isotopically labeled derivatives of disclosed compounds.

[0074] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid,

succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, naphthalene-***m,n***-bissulfonates, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, 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, salicylic acid, naphthalene-***m,n***-bissulfonic acids and the like.

[0075] Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_1\text{-}4alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate. 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, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0076] In certain embodiments, the pharmaceutically acceptable form is a solvate *(e.g.,* a hydrate). As used herein, the term "solvate" refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a "hydrate". Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or one to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term "compound" as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0077] In certain embodiments, the pharmaceutically acceptable form is an isomer. "Isomers" are different compounds that have the same molecular formula. "Atropisomers" are stereoisomers from hindered rotation about single bonds and can be resolved or isolated by methods known to those skilled in the art. For example, certain B substituents of a compound of Formula (I) provided herein with ortho or meta substituted phenyl may form atropisomers, where they may be separated and isolated.

[0078] "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. As used herein, the term "isomer" includes any and all geometric isomers and stereoisomers. For example, "isomers" include geometric double bond *cis-* and trans-isomers, also termed /•'- and Z- isomers; R- and *S*-enantiomers; diastereomers, (*d*)-isomers and (*l*)-isomers, racemic mixtures thereof; and other mixtures thereof, as falling within the scope of this disclosure.

[0079] In certain embodiments, the symbol ⁻⁻⁻⁻⁻⁻ denotes a bond that can be a single or double as described herein.

[0080] In certain embodiments, provided herein are various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*' are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "*E*" and "*Z*" isomers.

[0081] Substituents around a carbon-carbon double bond alternatively can be referred to as *"cis"* or *"trans,"* where *"cis"* represents substituents on the same side of the double bond and *"trans"* represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as *"cis"* or *"trans."* The term *"cis"* represents substituents on the same side of the plane of the ring, and the term *"trans"* represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of the plane of the ring are designated *"cis/trαns."*

[0082] "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as 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 can be specified according to the Cahn-Ingold-Prelog *R-S* system. When a compound is an 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 at each asymmetric atom, as (*R*)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures. Optically active (*R*)- and (S)- isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0083] The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below, a composition contains 90% of one enantiomer, e.g., an S enantiomer, and 10% of the other enantiomer, e.g., an *R* enantiomer.

$$ee = (90\text{-}10)/100 = 80\%.$$

[0084] Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. Some compositions described herein contain an enantiomeric excess of at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 75%, about 90%, about 95%, or about 99% of the S enantiomer. In other words, the compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. In other embodiments, some compositions described herein contain an enantiomeric excess of at least about 1%, about 5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 75%, about 90%, about 95%, or about 99% of the R enantiomer. In other words, the compositions contain an enantiomeric excess of the R enantiomer over the S enantiomer.

[0085] For instance, an isomer/enantiomer can, in some embodiments, be provided substantially free of the corresponding enantiomer, and can also be referred to as "optically enriched," "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used interchangeably herein. These terms refer to compositions in which the amount 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 about 50% by weight of the S enantiomer relative to the total weight of the preparation *(e.g.,* total weight of *S* and R isomers). such as at least about 75% by weight, further such as at least about 80% by weight. In some embodiments, the enrichment can be much greater than about 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 about 85% by weight of one enantiomer relative to the total weight of the preparation, such as at least about 90% by weight, and further such as at least about 95% by weight. In certain embodiments, the compound provided herein is made up of at least about 90% by weight of one enantiomer. In other embodiments, the compound is made up of at least about 95%, about 98%, or about 99% by weight of one enantiomer.

[0086] In some embodiments, the compound is a racemic mixture of (S)- and (R)- isomers. In other embodiments, provided herein is a mixture of compounds wherein individual compounds of the mixture exist predominately in an (S)- or (R)- isomeric configuration. For example, in some embodiments, the compound mixture has an (S)-enantiomeric excess of greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%. In some embodiments, the compound mixture has an (*S*)-enantiomeric excess of about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5%, or more. In some embodiments, the compound mixture has an (*S*)-enantiomeric excess of about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0087] In other embodiments, the compound mixture has an (*R*)-enantiomeric excess of greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%. In some embodiments, the compound mixture has an (*R*)-enantiomeric excess of about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5%, or more. In some embodiments, the compound mixture has an (*R*)-enantiomeric excess of about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to

about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0088] In other embodiments, the compound mixture contains identical chemical entities except for their stereochemical orientations, namely (S)- or (*R*)-isomers. For example, if a compound disclosed herein has -CH(R)-unit, and R is not hydrogen, then the -CH(R)- is in an (S)- or (*R*)- stereochemical orientation for each of the identical chemical entities *(i.e.,* (S)- or (*R*)-stereoisomers). In some embodiments, the mixture of identical chemical entities *(i.e.,* mixture of stereoisomers) is a racemic mixture of (S)- and (R)- isomers. In another embodiment, the mixture of the identical chemical entities *(i.e.,* mixture of stereoisomers) contains predominately (*S*)-isomer or predominately (R)-isomer. For example, in some embodiments, the (*S*)-isomer in the mixture of identical chemical entities *(i.e.,* mixture of stereoisomers) is present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5% by weight, or more, relative to the total weight of the mixture of (S)- and (R)-isomers. In some embodiments, the (*S*)-isomer in the mixture of identical chemical entities *(i.e.,* mixture of stereoisomers) is present at an (*S*)-enantiomeric excess of about 10% to about 99.5%, about 20% to about 99.5%, about 30% to about 99.5%, about 40% to about 99.5%, about 50% to about 99.5%, about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0089] In other embodiments, the (R)-isomer in the mixture of identical chemical entities *(i.e.,* mixture of stereoisomers) is present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.5% by weight, or more, relative to the total weight of the mixture of (S)- and (*R*)-isomers.. In some embodiments, the (R)-isomers in the mixture of identical chemical entities (i.e., mixture of stereoisomers) is present at an (*R*)-enantiomeric excess of about 10% to about 99.5%, about 20% to about 99.5%, about 30% to about 99.5%, about 40% to about 99.5%, about 50% to about 99.5%, about 55% to about 99.5%, about 60% to about 99.5%, about 65% to about 99.5%, about 70% to about 99.5%, about 75% to about 99.5%, about 80% to about 99.5%, about 85% to about 99.5%, about 90% to about 99.5%, about 95% to about 99.5%, about 96% to about 99.5%, about 97% to about 99.5%, about 98% to about 99.5%, or about 99% to about 99.5%, or more than about 99.5%.

[0090] Enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC), the formation and crystallization of chiral salts, or prepared by asymmetric syntheses. *See,* for example, Enantiomers, Racemates and Resolutions (Jacques, Ed., Wiley Interscience, New York, 1981); Wilen et al., Tetrahedron 33:2725 (1977); Stereochemistry of Carbon Compounds (E.L. Eliel, Ed., McGraw-Hill, NY, 1962); and Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0091] In certain embodiments, the pharmaceutically acceptable form is a tautomer. As used herein, the term "tautomer" is a type of isomer that includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (e.g., a single bond to a double bond, a triple bond to a double bond, or a triple bond to a single bond, or *vice versa).* "Tautomerization" 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. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible *(e.g.,* in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations *(i.e.,* the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent. Exemplary tautomerizations include, but are not limited to, keto-enol; amide-imide; lactam-lactim; enamine-imine; and enamine-(a different) enamine tautomerizations. 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.

[0092] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement or enrichment of a hydrogen by deuterium or tritium at one or more atoms in the molecule, or the replacement or enrichment of a carbon by ^{13}C or ^{14}C at one or more atoms in the molecule, are within the scope of this disclosure. In one embodiment, provided herein are isotopically labeled compounds having one or more hydrogen atoms replaced by or enriched by deuterium. In one embodiment, provided herein are isotopically labeled compounds having one or more hydrogen atoms replaced by or enriched by tritium. In one embodiment, provided herein are isotopically labeled compounds having one or more carbon atoms replaced or enriched by ^{13}C. In one embodiment, provided herein are isotopically labeled compounds having one or more carbon atoms replaced or enriched by ^{14}C.

[0093] The disclosure also embraces isotopically labeled compounds which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into disclosed compounds

include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, *e.g.,* ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Certain isotopically-labeled disclosed compounds *(e.g.,* those labeled with ^{3}H and/or ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated *(i.e.,* ^{3}H) and carbon-14 *(i.e.,* ^{14}C) isotopes can allow for ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium *(i.e.,* ^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability *(e.g.,* increased *in vivo* half-life or reduced dosage requirements). Isotopically labeled disclosed compounds can generally be prepared by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. In some embodiments, provided herein are compounds that can also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. All isotopic variations of the compounds as disclosed herein, whether radioactive or not, are encompassed within the scope of the present disclosure.

[0094] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. 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 as disclosed herein is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[0095] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Organic Chemistry, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March March's Advanced Organic Chemistry, 5th ed., John Wiley & Sons, Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd ed., Cambridge University Press, Cambridge, 1987.

[0096] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0097] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having, in some embodiments, from one to ten carbon atoms (e.g., C_1-C_{10} alkyl). Linear or straight alkyl refers to an alkyl with no branching, e.g., methyl, ethyl, n-propyl. 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 can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, an alkyl is a C_1-C_6 alkyl group. In some embodiments, alkyl groups have 1 to 10, 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0098] "Perhaloalkyl" refers to an alkyl group in which all of the hydrogen atoms have been replaced with a halogen selected from fluoro, chloro, bromo, and iodo. In some embodiments, all of the hydrogen atoms are each replaced with fluoro. In some embodiments, all of the hydrogen atoms are each replaced with chloro. Examples of perhaloalkyl groups include $-CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$ and the like. "Haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms have been replaced with a halogen independently selected from fluoro, chloro, bromo, and iodo.

[0099] "Alkyl-cycloalkyl" refers to an -(alkyl)cycloalkyl radical where alkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkyl and cycloalkyl respectively. The "alkyl-cycloalkyl" is bonded to the parent molecular structure through the alkyl group. The terms "alkenyl-cycloalkyl" and "alkynyl-cycloalkyl" mirror the above description of "alkyl-cycloalkyl" wherein the term

"alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[0100] "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. The "alkylaryl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)aryl" and "-(alkynyl)aryl" mirror the above description of "-(alkyl)aryl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[0101] "Alkyl-heteroaryl" refers to an -(alkyl)heteroaryl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and alkyl respectively. The "alkyl-heteroaryl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)heteroaryl" and "-(alkynyl)heteroaryl" mirror the above description of "-(alkyl)heteroaryl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[0102] "Alkyl-heterocyclyl" refers to an -(alkyl)heterocyclyl radical where alkyl and heterocyclyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocyclyl and alkyl respectively. The "alkyl-heterocyclyl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)heterocyclyl" and "-(alkynyl)heterocyclyl" mirror the above description of "-(alkyl)heterocyclyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[0103] "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 in some embodiments, 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 can consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkenyl). The alkenyl is attached to the parent molecular structure by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl *(i.e.,* allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4) and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless stated otherwise in the specification, an alkenyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0104] "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, in some embodiments, 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 can consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to five carbon atoms (*e.g.*, C_2-C_5 alkynyl). The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise in the specification, an alkynyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0105] The term "alkoxy" refers to the group -O-alkyl (in some embodiments, including from 1 to 10 carbon atoms), of a straight, branched, cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. "Lower

alkoxy" refers to alkoxy groups containing one to six carbons. In some embodiments, C_1-C_4 alkoxy is an alkoxy group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxy group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "alkenoxy" and "alkynoxy" mirror the above description of "alkoxy" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

[0106] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached to the parent molecular structure through the carbonyl carbon (in some embodiments, having from 1 to 10 carbon atoms). Thus a C_1-C_6 alkoxycarbonyl group comprises an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. The C_1-C_6 designation does not include the carbonyl carbon in the atom count. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkyl portion of the alkoxy group is a lower alkyl group. In some embodiments, C_1-C_4 alkoxycarbonyl comprises an alkoxy group which encompasses both straight and branched chain alkoxy groups of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxycarbonyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "alkenoxycarbonyl" and "alkynoxycarbonyl" mirror the above description of "alkoxycarbonyl" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

[0107] "Acyl" refers to R-C(O)- groups such as, but not limited to, H, (alkyl)-C(O)-, (alkenyl)-C(O)-, (alkynyl)-C(O)-, (aryl)-C(O)-, (cycloalkyl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)-, and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent molecular structure through the carbonyl functionality. In some embodiments, provided herein is a C_1-C_{10} acyl radical which refers to the total number of chain or ring atoms of the, for example, alkyl, alkenyl, alkynyl, aryl, cyclohexyl, heteroaryl or heterocycloalkyl portion plus the carbonyl carbon of acyl. For example, a C_4-acyl has three other ring or chain atoms plus carbonyl. 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 in the specification, the "R" of an acyloxy group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0108] "Acyloxy" refers to a R(C=O)O- radical wherein "R" can be H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cyclohexyl, heteroaryl, or heterocycloalkyl, which are as described herein. The acyloxy group is attached to the parent molecular structure through the oxygen functionality. In some embodiments, an acyloxy group is a C_1-C_4 acyloxy radical which refers to the total number of chain or ring atoms of the alkyl, alkenyl, alkynyl, aryl, cyclohexyl, heteroaryl or heterocycloalkyl portion of the acyloxy group plus the carbonyl carbon of acyl, *e.g.,* a C_4-acyloxy has three other ring or chain atoms plus carbonyl. 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 in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mer-

capto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl and each of these moieties can be optionally substituted as defined herein.

[0109] "Amino" or "amine" refers to a $-N(R^b)_2$, $-N(R^b)R^b-$, or $-R^bN(R^b)_R{}^b-$ radical group, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. When a $-N(R^b)_2$ group has two R^b other than hydrogen, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, 7-, or 8-membered ring. For example, $-N(R^b)_2$ is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise in the specification, an amino group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0110] The terms "amine" and "amino" can also refer to N-oxides of the groups $-N^+(H)(R^a)O^-$, and $-N^+(R^a)(R^a)O^-$, where R^a is as described above, where the N-oxide is bonded to the parent molecular structure through the N atom. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid. The person skilled in the art is familiar with reaction conditions for carrying out the N-oxidation.

[0111] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R^b)_2$ or $-NR^bC(O)R^b$, where R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, an amido or amide radical is a C_1-C_4 amido or amide radical, which includes the amide carbonyl in the total number of carbons in the radical. When a $-C(O)N(R^b)_2$ has two R^b other than hydrogen, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, 7-, or 8-membered ring. For example, $N(R^b)_2$ portion of a $-C(O)N(R^b)_2$ radical is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise in the specification, an amido R^b group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0112] The term "amide" or "amido" is inclusive of an amino acid or a peptide molecule. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be transformed into an amide group. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 4th Ed., John Wiley & Sons, New York, NY, 2006.

[0113] "Amidino" refers to the $-C(=NR^b)N(R^b)_2$, $-N(R^b)-C(=NR^b)-R^b$, and $-N(R^b)-C(=NR^b)-$ radicals, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0114] "Aryl" refers to a radical with six to fourteen ring atoms *(e.g.,* C_6-C_{14} or C_6-C_{10} aryl) which has at least one carbocyclic ring having a conjugated pi electron system which is aromatic (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) (e.g., phenyl, fluorenyl, and naphthyl). In one embodiment, bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. In other embodiments, bivalent radicals derived from univalent monocyclic or 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 aryl" refers to each integer in the given range; *e.g.,* "6 to 10 ring atoms" means that the aryl group can 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 in the specification, an aryl moiety can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In one embodiment, unless stated otherwise, "aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the aryl ring.

[0115] "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. The "aralkyl" or "arylalkyl" is bonded to the parent molecular structure through the alkyl group. The terms "aralkenyl/arylalkenyl" and "aralkynyl/arylalkynyl" mirror the above description of "aralkyl/arylalkyl" wherein the "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and the "alkenyl" or "alkynyl" terms are as described herein.

[0116] "Azide" refers to a $-N_3$ radical.

[0117] "Carbamate" refers to any of the following radicals: $-O-(C=O)-N(R^b)-$, $-O-(C=O)-N(R^b)_2$, $-N(R^b)-(C=O)-O-$, and $-N(R^b)-(C=O)-OR^b$, wherein each R^b is independently selected from H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0118] "Carbonate" refers to a $-O-(C=O)-O-$ or $-O-(C=O)-OR$ radical, where R can be hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cyclohexyl, heteroaryl, or heterocycloalkyl, which are as described herein.

[0119] "Carbonyl" refers to a $-(C=O)-$ radical.

[0120] "Carboxaldehyde" refers to a $-(C=O)H$ radical.

[0121] "Carboxyl" refers to a $-(C=O)OH$ radical.

[0122] "Cyano" refers to a -CN radical.

[0123] "Cycloalkyl," or alternatively, "carbocyclyl," refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Partially unsaturated cycloalkyl groups can be termed "cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle contains at least one triple bond. Cycloalkyl groups include groups having from 3 to 10 ring atoms *(e.g.,* C_3-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 can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 10 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic *(i.e.,* rings which share adjacent pairs of ring atoms) groups. In some embodiments, it is a C_3-C_8 cycloalkyl radical. In some embodiments, it is a C_3-C_5 cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Examples of C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), bicyclo[2.2. 1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as octahydro-1*H*-indenyl, decahydronaphthalenyl, spiro[4.5]decanyl, and the like. Unless stated otherwise in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties

can be optionally substituted as defined herein. In one embodiment, unless stated otherwise, "cycloalkyl" or "carbocyclyl" also includes ring systems wherein the cycloalkyl or carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment to the parent molecular structure is on the cycloalkyl or carbocyclyl ring.

[0124] "Cycloalkyl-alkyl" refers to a -(cycloalkyl)alkyl radical where cycloalkyl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkyl respectively. The "cycloalkyl-alkyl" is bonded to the parent molecular structure through the cycloalkyl group. The terms "cycloalkyl-alkenyl" and "cycloalkyl-alkynyl" mirror the above description of "cycloalkyl-alkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[0125] "Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl)heterocyclylalkyl 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 heterocycloalkyl and cycloalkyl respectively. The "cycloalkyl-heterocycloalkyl" is bonded to the parent molecular structure through the cycloalkyl group.

[0126] "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 heteroaryl and cycloalkyl respectively. The "cycloalkyl-heteroaryl" is bonded to the parent molecular structure through the cycloalkyl group.

[0127] As used herein, a "covalent bond" or "direct bond" refers to a single bond joining two groups.

[0128] "Ester" refers to a radical of formula -COOR, where R is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 4th Ed., John Wiley & Sons, New York, NY, 2006. Unless stated otherwise in the specification, an ester group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0129] "Ether" refers to a $-R^b-O-R^b$ radical where each R^b is independently selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0130] "Halo", "halide", or, alternatively, "halogen" means 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, such as, but not limited to, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. Each of the alkyl, alkenyl, alkynyl and alkoxy groups are as defined herein and can be optionally further substituted as defined herein.

[0131] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include alkyl, alkenyl and alkynyl radicals, respectively, which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, and phosphorus, or combinations thereof. A numerical range can be given, *e.g.,* C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example can be up to 4 atoms long. For example, a $-CH_2OCH_2CH_3$ radical is referred to as a "C_4" heteroalkyl, which includes the heteroatom center in the atom chain length description. Connection to the parent molecular structure can be through either a heteroatom or a carbon in the heteroalkyl chain. For example, an *N*-containing heteroalkyl moiety refers to a group in which at least one of the skeletal atoms is a nitrogen atom. One or more heteroatom(s) in the heteroalkyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. For example, heteroalkyl also includes skeletal chains substituted with one or more nitrogen oxide (-O-) substituents. Exemplary heteroalkyl groups include, without limitation, ethers such as methoxyethanyl ($-CH_2CH_2OCH_3$), ethoxymethanyl ($-CH_2OCH_2CH_3$), (methoxymethoxy)ethanyl ($-CH_2CH_2-OCH_2OCH_3$), (methoxymethoxy)methanyl ($-CH_2OCH_2OCH_3$), and (methoxyethoxy)methanyl ($-CH_2OCH_2CH_2OCH_3$), and the like; amines such as $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2NHCH_2CH_3$, $-CH_2N(CH_2CH_3)(CH_3)$, and the like. Heteroalkyl, heteroalkenyl, and heteroalkynyl groups can each be optionally substituted by one or more substituents which independently include:

acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0132] "Heteroalkyl-aryl" refers to a -(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. The "heteroalkyl-aryl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[0133] "Heteroalkyl-heteroaryl" refers to a -(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. The "heteroalkyl-heteroaryl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[0134] "Heteroalkyl-heterocycloalkyl" refers to a -(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. The "heteroalkyl-heterocycloalkyl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[0135] "Heteroalkyl-cycloalkyl" refers to a -(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. The "heteroalkyl-cycloalkyl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[0136] "Heteroaryl", or alternatively, "heteroaromatic", refers to a radical of a 5- to 18-membered monocyclic or polycyclic *(e.g.,* bicyclic or tricyclic) aromatic ring system *(e.g.,* having 6, 10 or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1 to 6 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 18-membered heteroaryl"). Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or more rings. 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 can consist of 5 ring atoms, 6 ring atoms, 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, etc., up to and including 18 ring atoms. In one embodiment, 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.

[0137] For example, an 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. One or more heteroatom(s) in the heteroaryl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. Heteroaryl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as pyridinyl N-oxides. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s).

[0138] "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment to the parent molecular structure is either on the aryl or on the heteroaryl ring, or wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the heteroaryl ring. For polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl and the like), the point of attachment to the parent molecular structure can be on either the ring bearing a heteroatom *(e.g.,* 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). In some embodiments, a heteroaryl group is a 5 to 10 membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 10-membered heteroaryl"). In some embodiments, a heteroaryl group is a 5- to 8-membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 8-membered heteroaryl"). In some embodiments, a heteroaryl group is a 5- to 6-membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 6-membered heteroaryl"). In some embodiments, the 5- to 6-membered heteroaryl has 1 to 3 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heteroaryl has 1 to 2 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous,

and sulfur.

[0139] 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]quinazoliny1, 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-1*H*-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]pridinyl, and thiophenyl *(i.e.,* thienyl).

[0140] Unless stated otherwise in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0141] "Heteroaryl-alkyl" refers to a -(heteroaryl)alkyl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and alkyl respectively. The "heteroaryl-alkyl" is bonded to the parent molecular structure through any atom of the heteroaryl group.

[0142] "Heteroaryl-heterocycloalkyl" refers to an -(heteroaryl)heterocycloalkyl radical where heteroaryl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and heterocycloalkyl respectively. The "heteroaryl-heterocycloalkyl" is bonded to the parent molecular structure through an atom of the heteroaryl group.

[0143] "Heteroaryl-cycloalkyl" refers to an -(heteroaryl)cycloalkyl radical where heteroaryl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and cycloalkyl respectively. The "heteroaryl-cycloalkyl" is bonded to the parent molecular structure through a carbon atom of the heteroaryl group.

[0144] "Heterocyclyl", "heterocycloalkyl" or 'heterocarbocyclyl" each refer to any 3-to 18-membered non-aromatic radical monocyclic or polycyclic moiety comprising at least one ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur. A heterocyclyl group can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein the polycyclic ring systems can be a fused, bridged or spiro ring system. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or more rings. A heterocyclyl group can be saturated or partially unsaturated. Partially unsaturated heterocycloalkyl groups can be termed "heterocycloalkenyl" if the heterocyclyl contains at least one double bond, or "heterocycloalkynyl" if the heterocyclyl contains at least one triple bond. 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 heterocyclyl group can consist of 5 ring atoms, 6 ring atoms, 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, etc., up to and including 18 ring atoms. In one embodiment, bivalent radicals derived from univalent heterocyclyl 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 piperidyl group with two points of attachment is a piperidylidene.

[0145] An N-containing heterocyclyl moiety refers to an non-aromatic group in which at least one of the ring atoms is a nitrogen atom. The heteroatom(s) in the heterocyclyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can be optionally quaternized. Heterocyclyl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as piperidinyl N-oxides. The heterocyclyl is attached to the parent molecular structure through any atom of any of the ring(s).

[0146] "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or

more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment to the parent molecular structure is on the heterocyclyl ring. In some embodiments, a heterocyclyl group is a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("3-to 10-membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5- to 8-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 8-membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5- to 6-membered heterocyclyl"). In some embodiments, the 5- to 6-membered heterocyclyl has 1 to 3 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heterocyclyl has 1 to 2 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5- to 6-membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

[0147] Exemplary 3-membered heterocyclyls containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4-membered heterocyclyls containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyls containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyls containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyls containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl, and triazinanyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0148] Unless stated otherwise, heterocyclyl moieties are optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (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 $-O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0149] "Heterocyclyl-alkyl" refers to a -(heterocyclyl)alkyl radical where heterocyclyl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocyclyl and alkyl respectively. The "heterocyclyl-alkyl" is bonded to the parent molecular structure through any atom of the heterocyclyl group. The terms "heterocyclyl-alkenyl" and "heterocyclyl-alkynyl" mirror the above description of "heterocyclyl-alkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[0150] "Imino" refers to the "$-C(=N-R^b)-R^b$" radical where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0151] "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.

[0152] "Nitro" refers to the $-NO_2$ radical.

[0153] "Oxa" refers to the -O- radical.

[0154] "Oxo" refers to the =O radical.

[0155] "Phosphate" refers to a -O-P(=O)(OR^b)$_2$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

[0156] "Phosphonate" refers to a -O-P(=O)(R^b)(OR^b) radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

[0157] "Phosphinate" refers to a -P(=O)(R^b)(OR^b) radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

[0158] A "leaving group or atom" is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable non-limiting examples of such groups, unless otherwise specified, include halogen atoms, mesyloxy, p-nitrobenzensulphonyloxy, trifluoromethyloxy, and tosyloxy groups.

[0159] "Protecting group" has the meaning conventionally associated with it in organic synthesis, *e.g.,* 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 such that the group can readily be 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, Fourth Edition, John Wiley & Sons, New York (2006). For example, a hydroxy protected form is where at least one of the hydroxy groups present in a compound is protected with a hydroxy protecting group. Likewise, amines and other reactive groups can similarly be protected.

[0160] As used herein, the terms "substituted" or "substitution" mean that at least one hydrogen present on a group atom *(e.g.,* a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution for the hydrogen results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group can have a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. Substituents can include one or more group(s) individually and independently selected from acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, azide, carbonate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^a)$_3$, -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), and -O-P(=O)(OR^a)$_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. For example, a cycloalkyl substituent can have a halide substituted at one or more ring carbons, and the like. The protecting groups that can form the protective derivatives of the above substituents are known to those of skill in the art and can be found in references such as Greene and Wuts, above.

[0161] "Silyl" refers to a -Si(R^b)$_3$ radical where each R^b is independently selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0162] "Sulfanyl", "sulfide", and "thio" each refer to the radical -S-R^b, wherein R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. For instance, an "alkylthio" refers to the "alkyl-S-" radical, and "arylthio" refers to the "aryl-S-" radical, each of which are bound to the parent molecular group through the S atom. The terms "sulfide", "thiol", "mercapto", and "mercaptan" can also each refer to the group -R^bSH.

[0163] "Sulfinyl" or "sulfoxide" refers to the -S(O)-R^b radical, wherein for "sulfinyl", R^b is H, and for "sulfoxide", R^b is

selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0164] "Sulfonyl" or "sulfone" refers to the $-S(O_2)-R^b$ radical, wherein R^b is selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0165] "Sulfonamidyl" or "sulfonamido" refers to the following radicals: $-S(=O)_2-N(R^b)_2$, $-N(R^b)-S(=O)_2-R^b$, $-S(=O)_2-N(R^b)-$, or $-N(R^b)-S(=O)_2-$, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. The R^b groups in $-S(=O)_2-N(R^b)_2$ or $-N(R^b)-S(=O)_2-R^b$ can be taken together with the nitrogen to which they are attached to form a 4-, 5-, 6-, 7-, or 8-membered heterocyclyl ring. In some embodiments, the term designates a C_1-C_4 sulfonamido, wherein each R^b in the sulfonamido contains 1 carbon, 2 carbons, 3 carbons, or 4 carbons total.

[0166] "Sulfoxyl" refers to a $-S(=O)_2OH$ radical.

[0167] "Sulfonate" refers to a $-S(=O)_2-OR^b$ radical, wherein R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0168] "Thiocarbonyl" refers to a -(C=S)- radical.

[0169] "Urea" refers to a $-N(R^b)-(C=O)-N(R^b)_2$ or $-N(R^b)-(C=O)-N(R^b)-$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon), and heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0170] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, $-CH_2O-$ is equivalent to $-OCH_2-$.

Compounds

[0171] In certain embodiments, provided herein is a mixture of compounds of Formula (I) or (A) wherein individual compounds of the mixture exist predominately in an (S)- or (R)- isomeric configuration. For example, the compound mixture has an (S)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In other embodiments, the compound mixture has an (S)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[0172] In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In some other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[0173] In certain embodiments, the compound of Formula (I) or (A) is in an (S)-stereochemical configuration.

[0174] In certain embodiments, the compound of Formula (I) or (A) is the S-enantiomer having an enantiomeric purity greater than 75%.

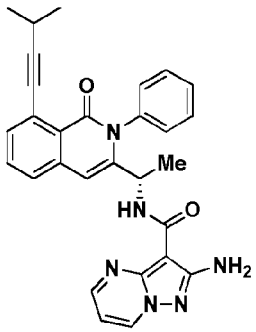
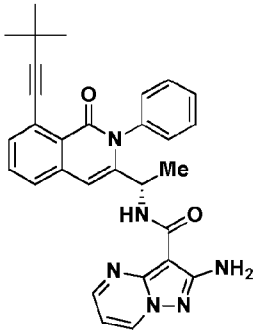
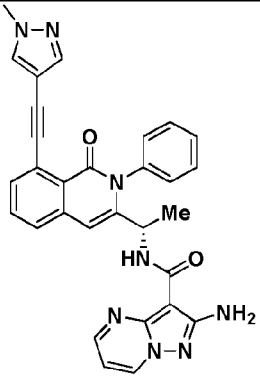
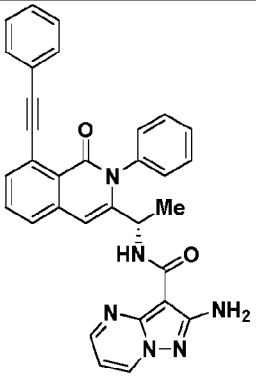
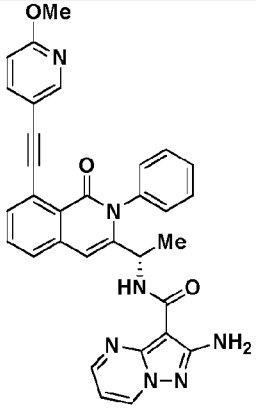
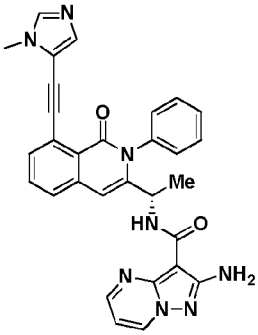
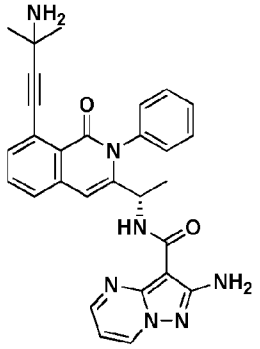
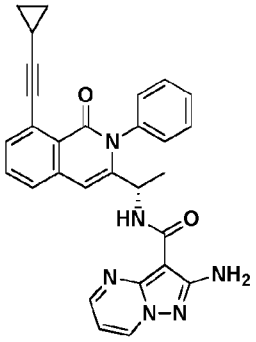
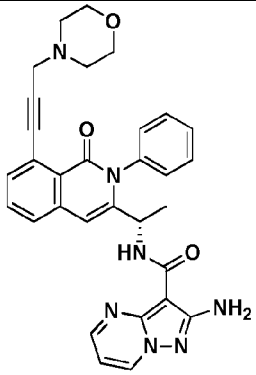
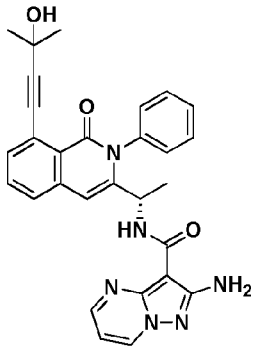
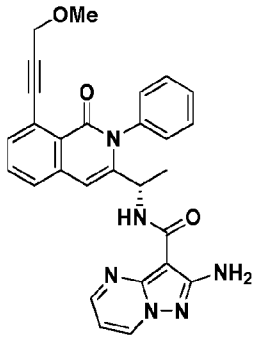
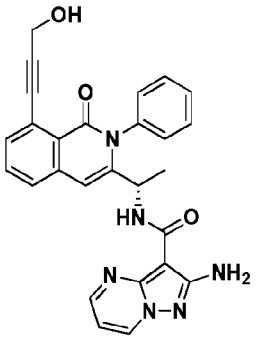
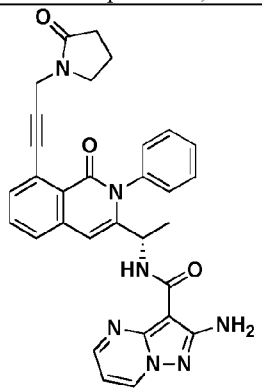
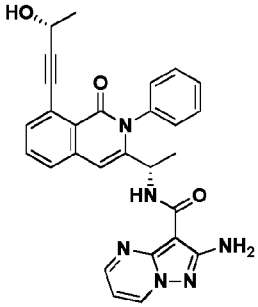
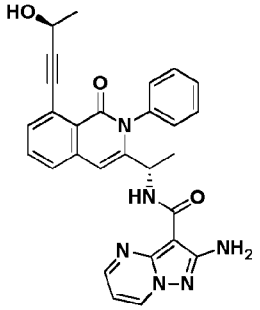
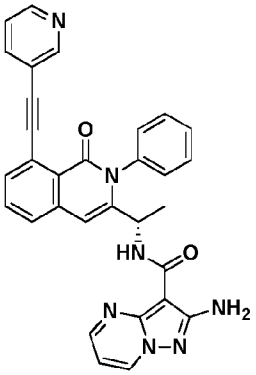
[0175] In certain embodiments, the compound of Formula (I) or (A) is a compound in Table 3, Table 4, Table 11 or Table 12, or a pharmaceutically acceptable form thereof.

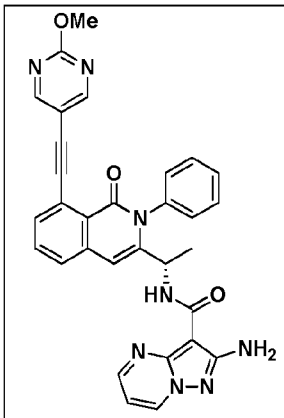
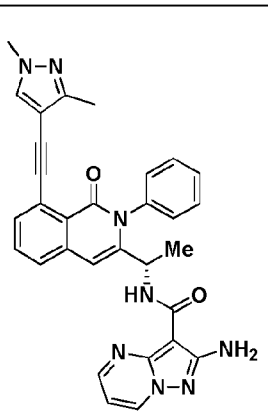
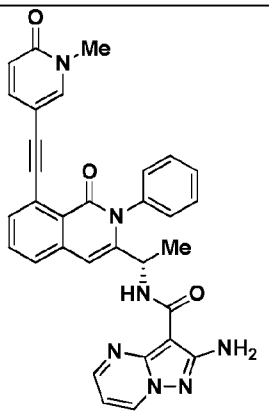
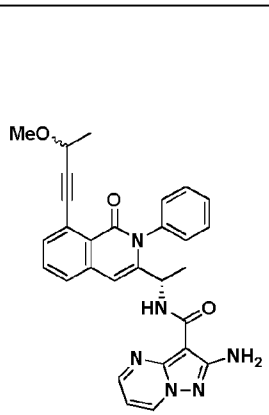
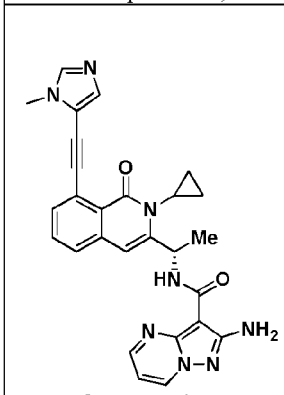
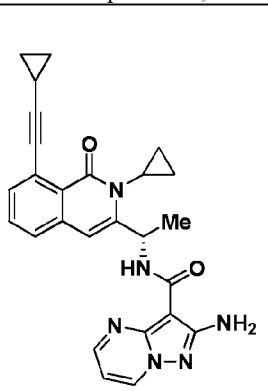
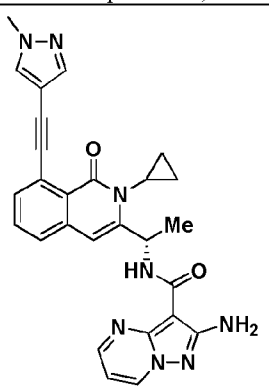
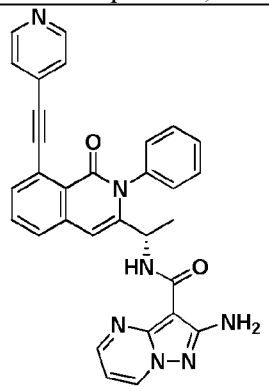
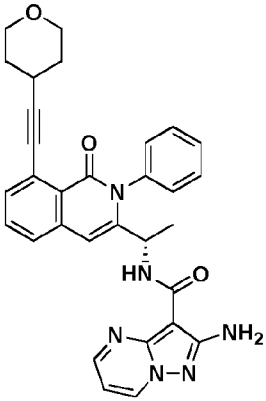
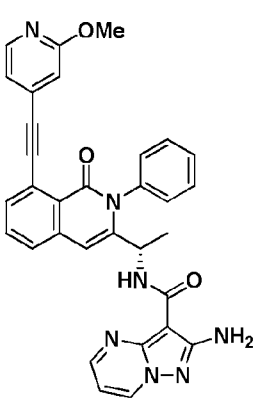
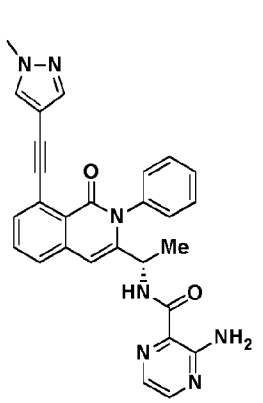
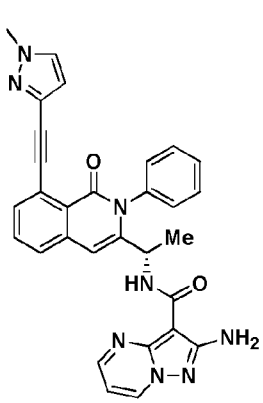
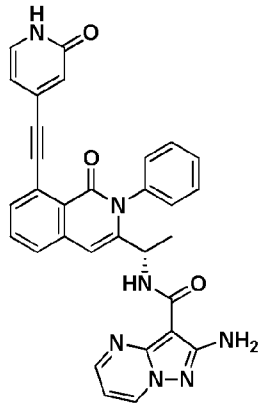
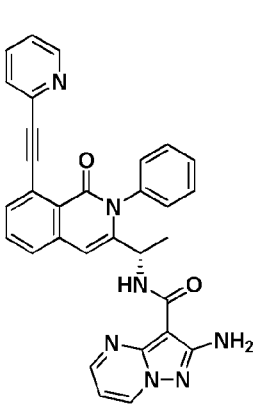
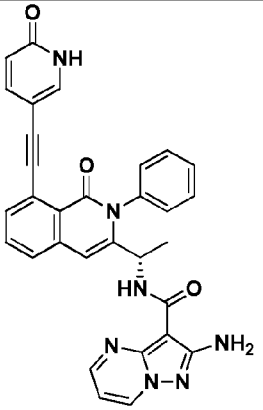
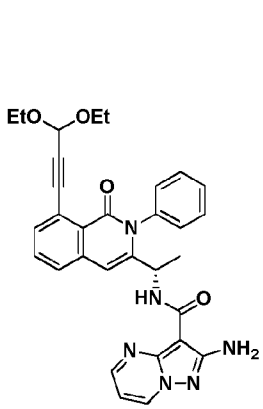
[0176] In certain embodiments, the compound of Formula (I) or (A) is a compound in Table 3 or Table 4 or a pharmaceutically acceptable form thereof.

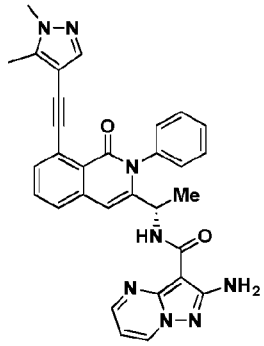
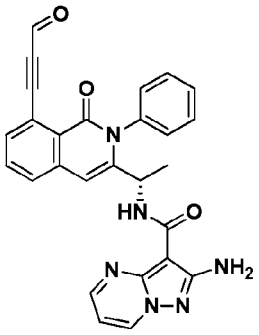
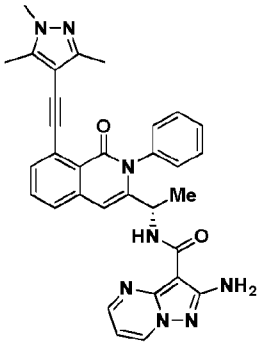
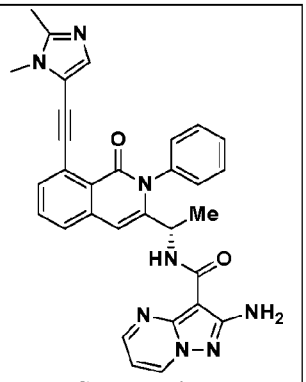
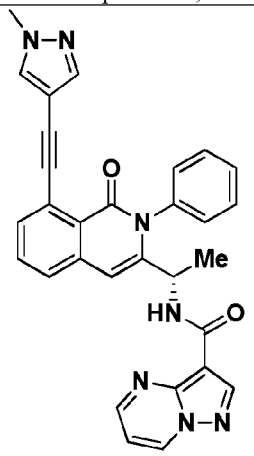
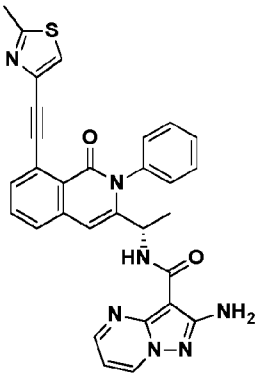
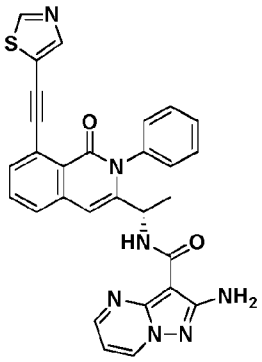
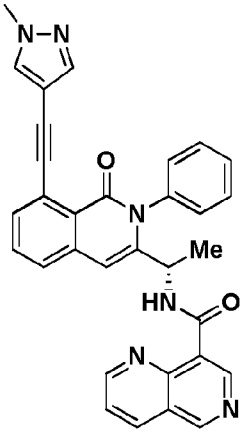
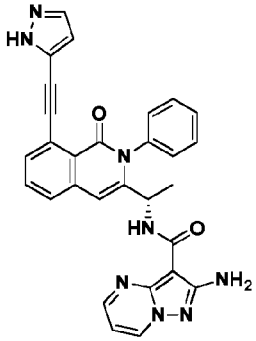
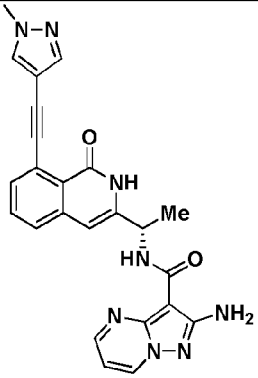
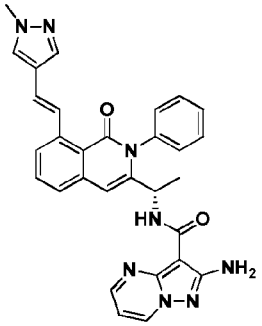
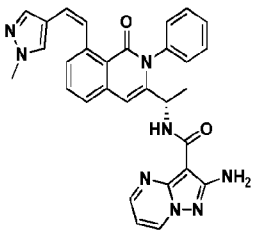
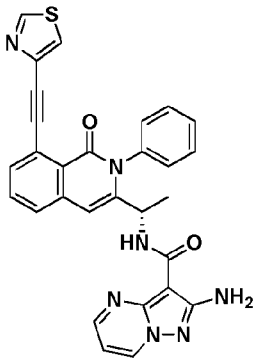
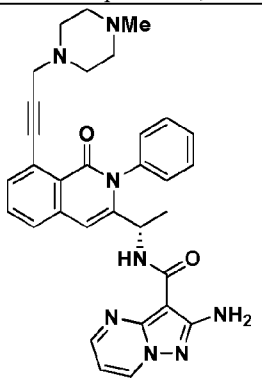
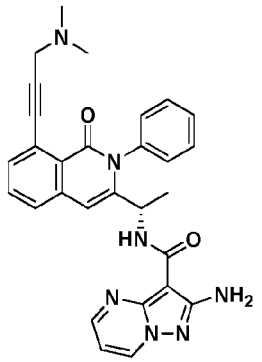
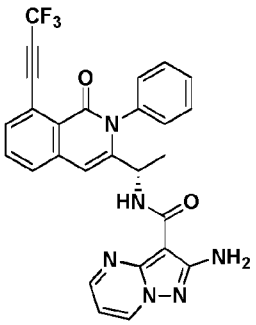
[0177] In certain embodiments, the compound of Formula (I) or (A) is a compound in Table 11 or a pharmaceutically acceptable form thereof.

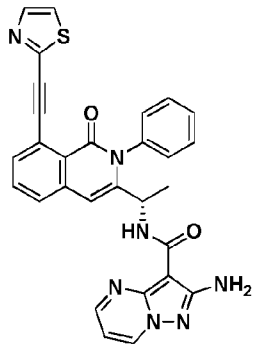
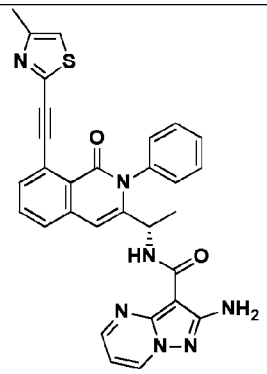
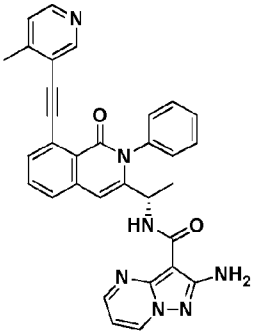
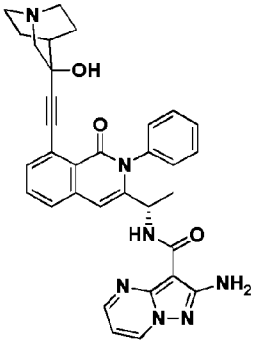
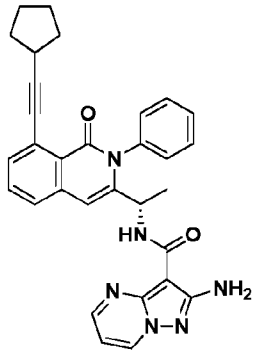
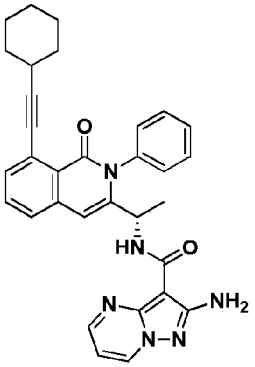
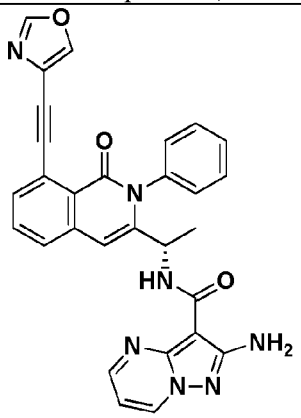
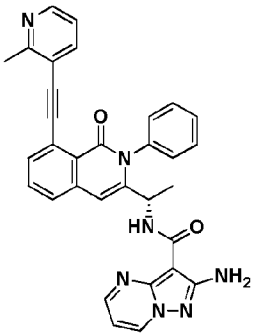
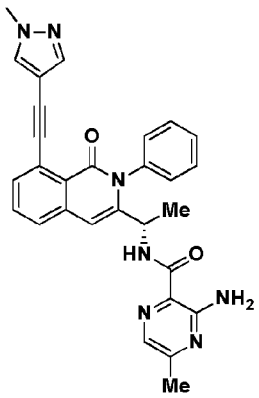
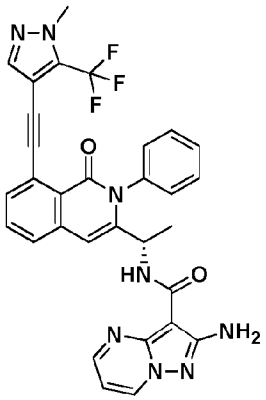
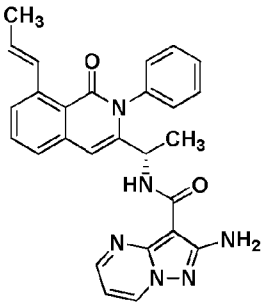
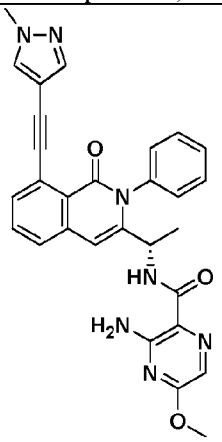
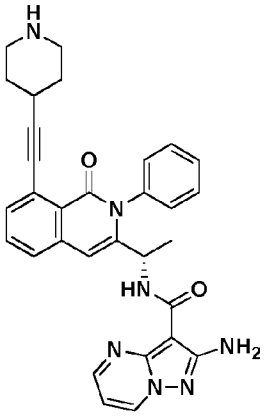
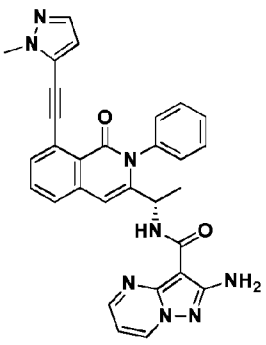
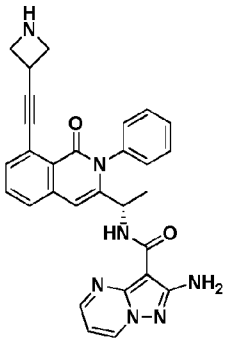
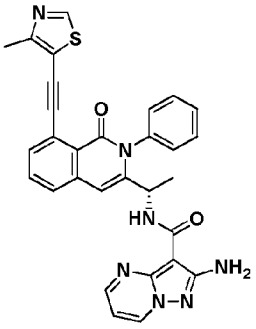
[0178] In certain embodiments, the compound of Formula (I) or (A) is a compound in Table 12 or a pharmaceutically acceptable form thereof.

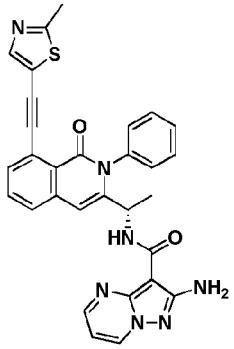
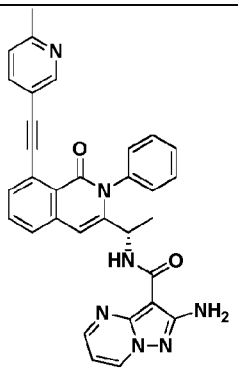
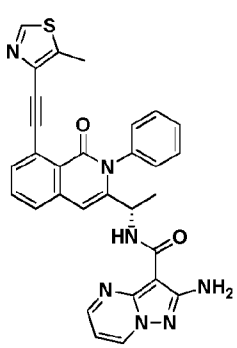
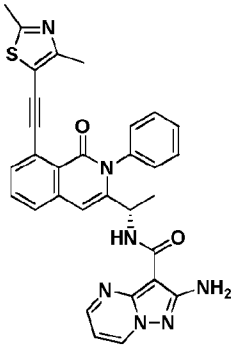
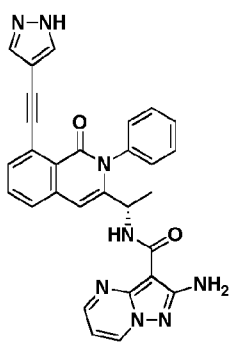
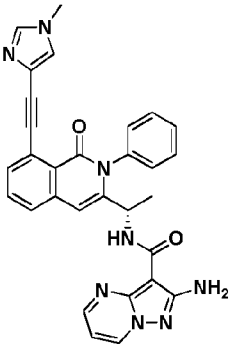
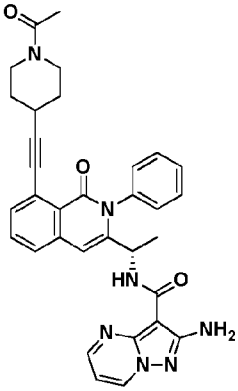
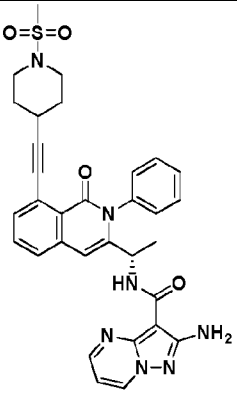
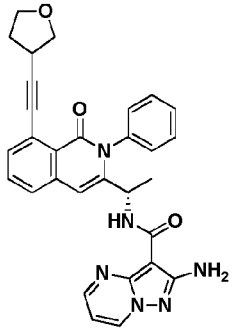
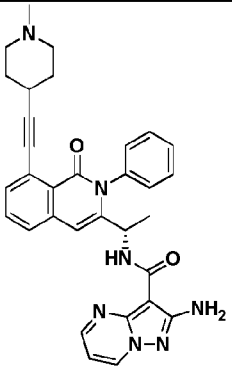
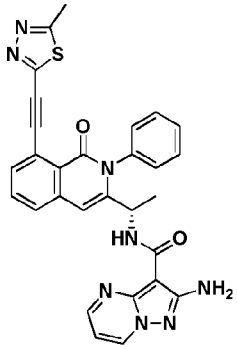
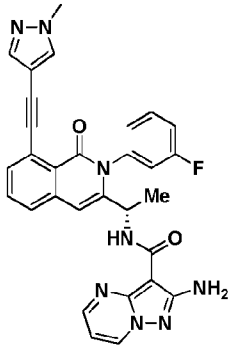
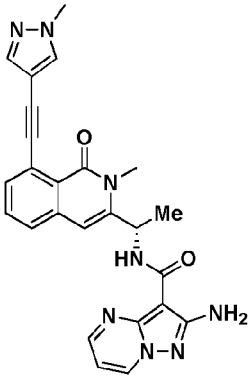
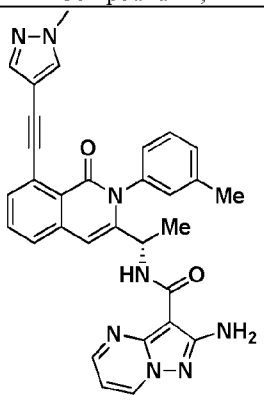
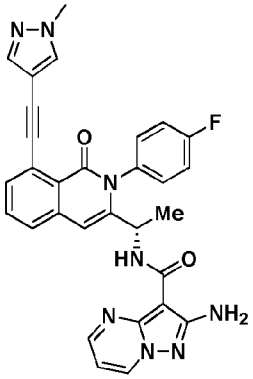
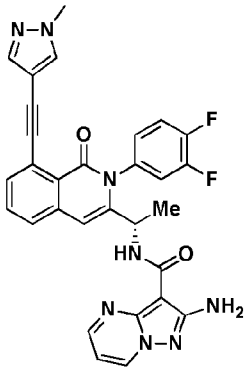
Table 3

 Compound 2,	 Compound 3,	 Compound 4,	 Compound 5,
 Compound 6,	 Compound 7,	 Compound 8,	 Compound 9,
 Compound 10,	 Compound 11,	 Compound 12,	 Compound 13,
 Compound 14,	 Compound 15,	 Compound 16,	 Compound 17,

 Compound 18,	 Compound 19,	 Compound 20,	 Compound 22,
 Compound 23,	 Compound 24,	 Compound 25,	 Compound 26,
 Compound 27,	 Compound 28,	 Compound 29,	 Compound 30,
 Compound 31,	 Compound 32,	 Compound 33,	 Compound 34,

 Compound 35,	 Compound 36,	 Compound 37,	 Compound 38,
 Compound 39,	 Compound 40,	 Compound 41,	 Compound 42,
 Compound 43,	 Compound 44,	 Compound 52,	 Compound 53,
 Compound 54.	 Compound 56,	 Compound 57,	 Compound 58,

 Compound 59,	 Compound 60,	 Compound 61,	 Compound 62,
 Compound 64,	 Compound 65,	 Compound 66,	 Compound 67,
 Compound 68,	 Compound 69,	 Compound 70,	 Compound 71,
 Compound 72,	 Compound 73,	 Compound 74,	 Compound 75,

 Compound 76,	 Compound 77,	 Compound 78,	 Compound 79,
 Compound 80,	 Compound 81,	 Compound 82,	 Compound 83,
 Compound 84,	 Compound 85,	 Compound 86,	 Compound 93,
 Compound 94,	 Compound 95,	 Compound 96,	 Compound 97,

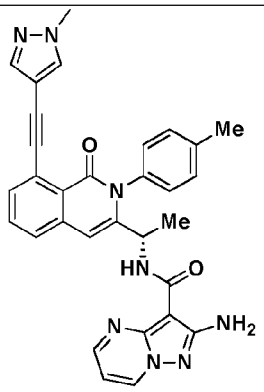
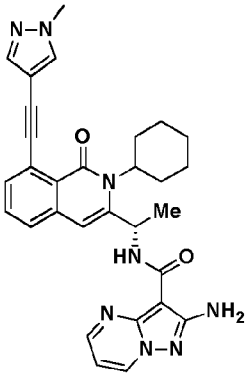
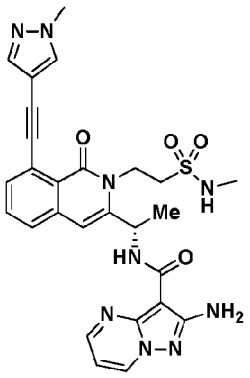
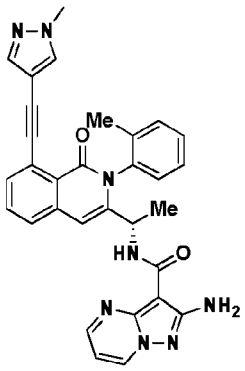
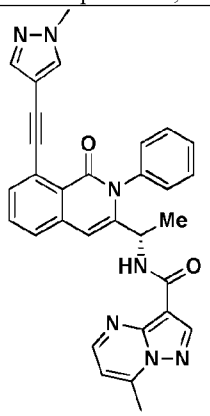
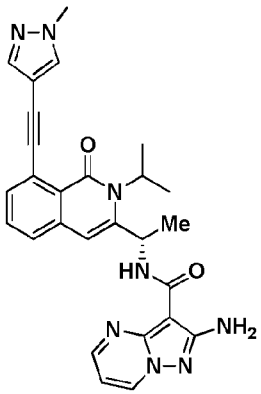
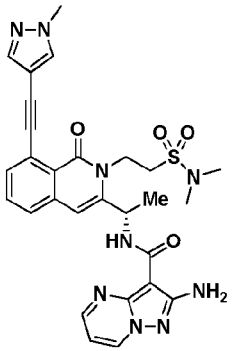
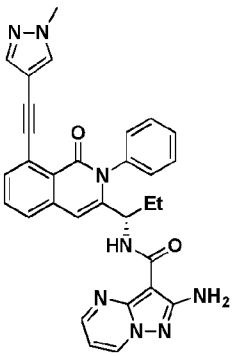
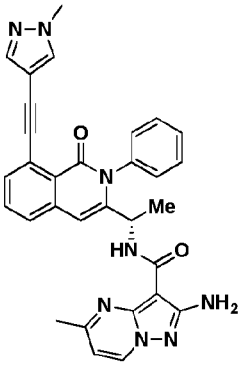
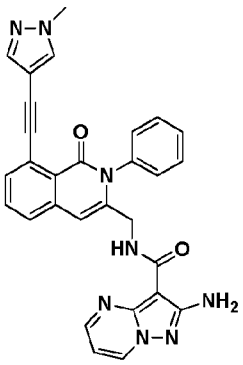
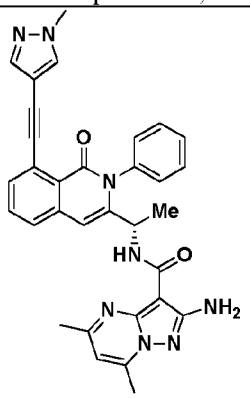
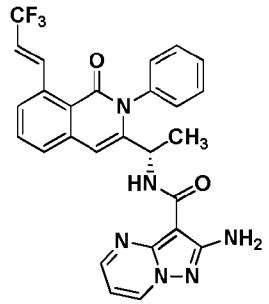
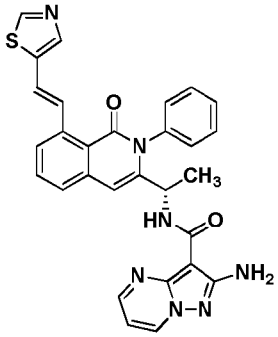
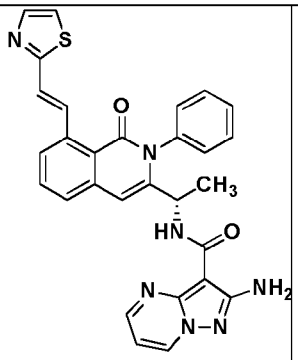
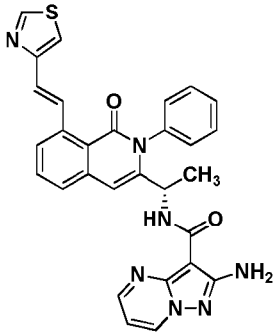
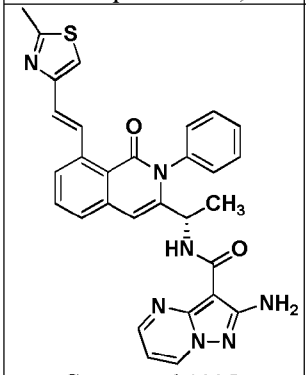
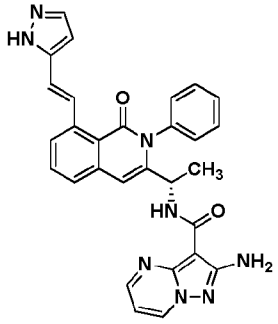
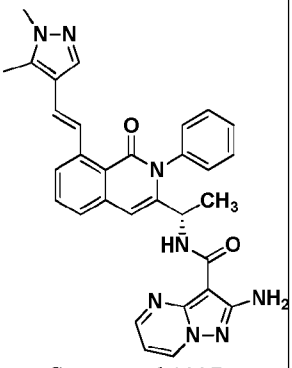
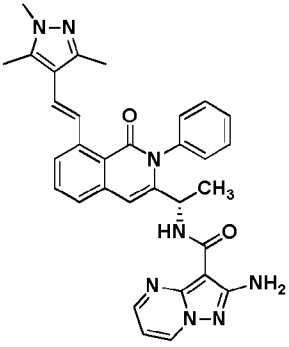
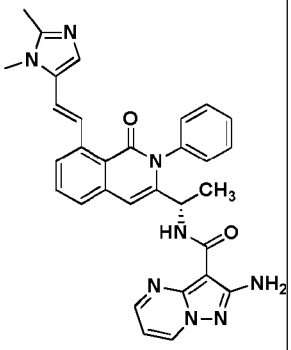
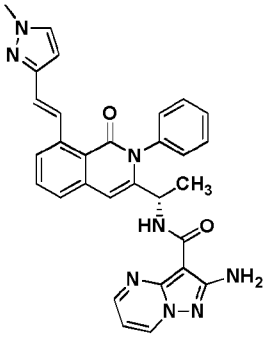
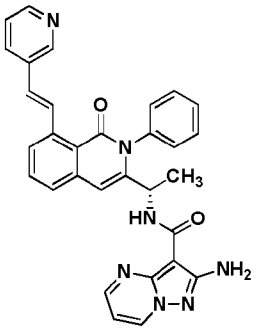
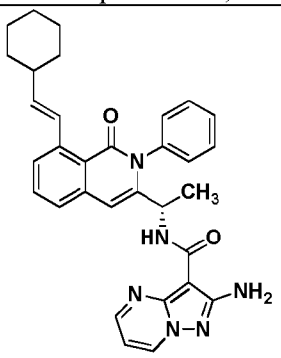
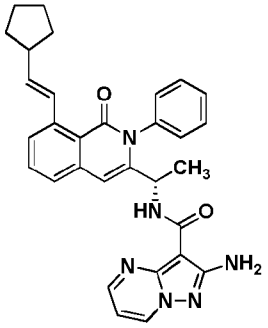
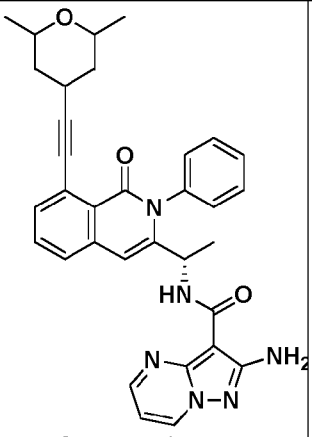
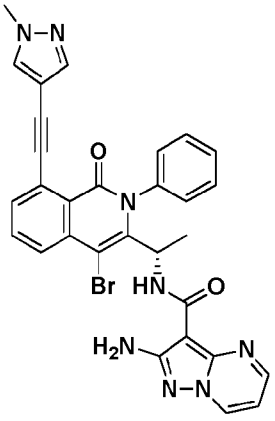
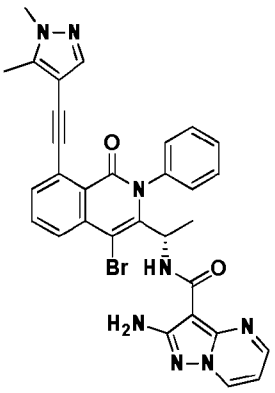
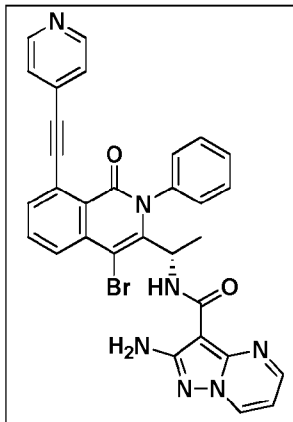
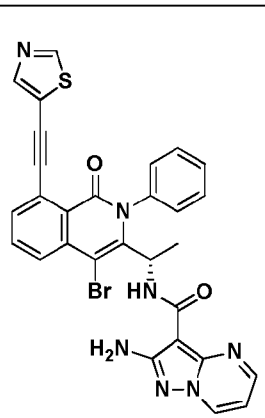
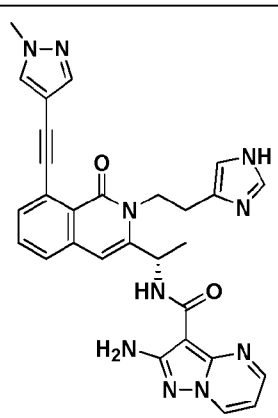
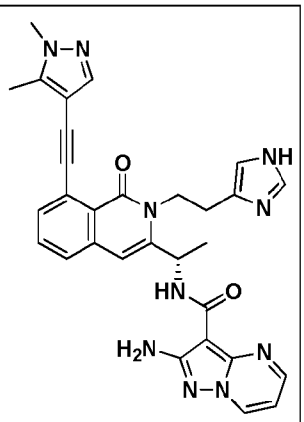
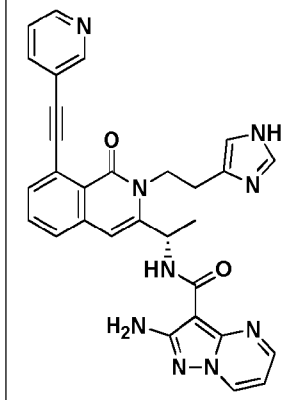
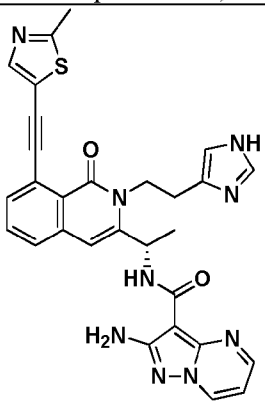
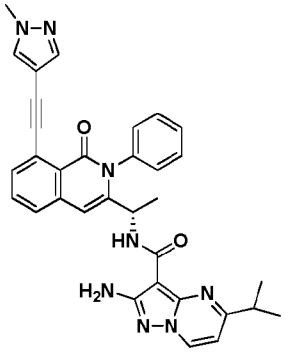
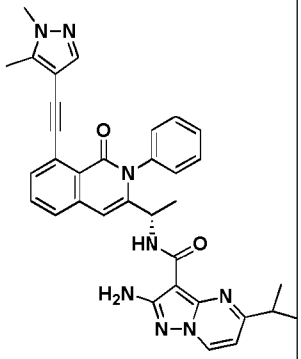
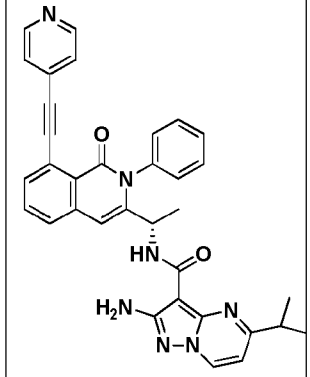
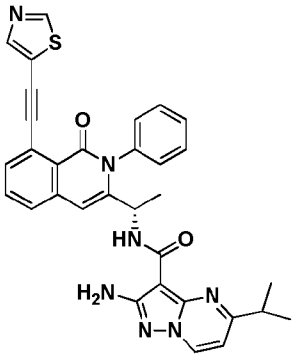
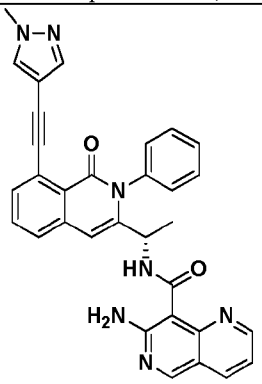
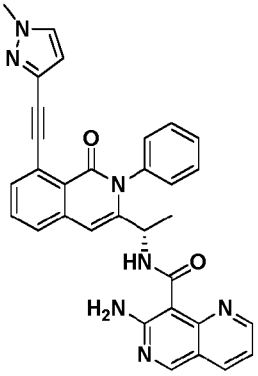
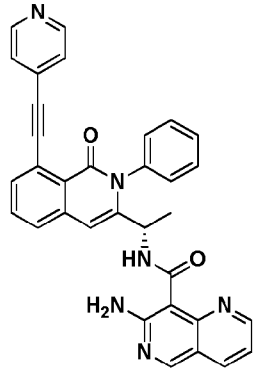
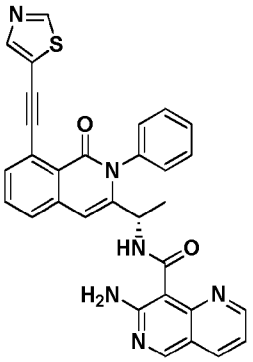
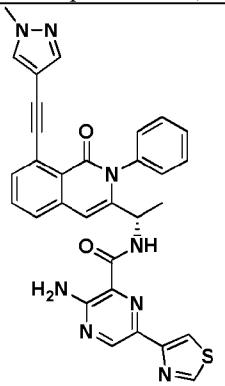
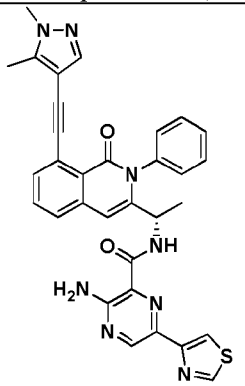
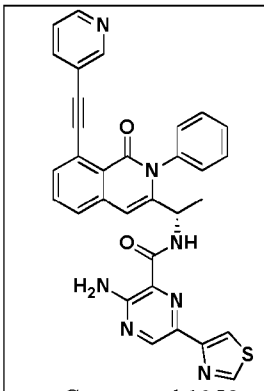
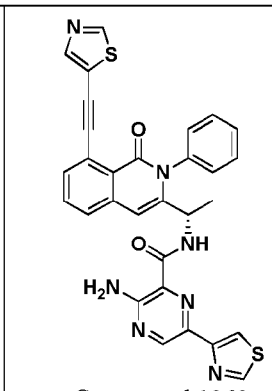
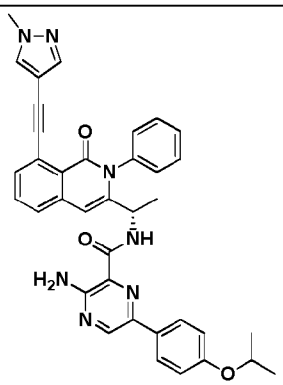
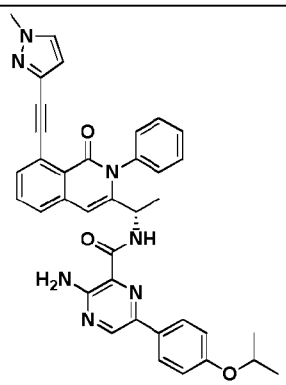
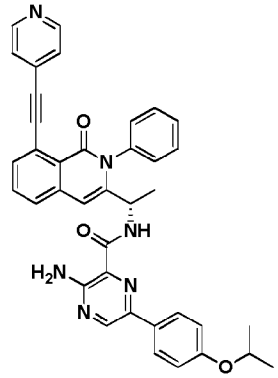
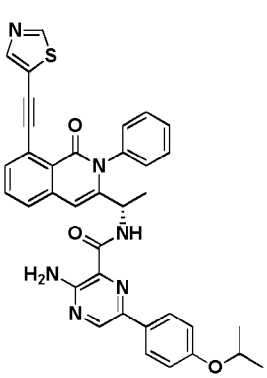
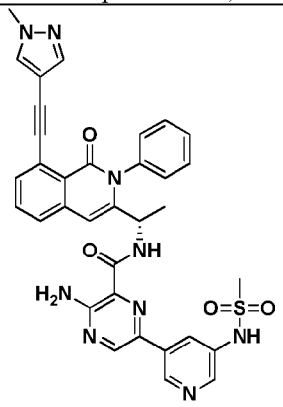
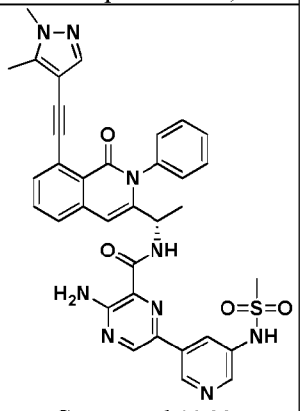
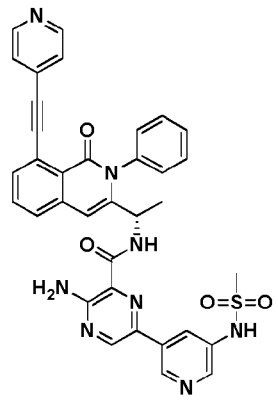
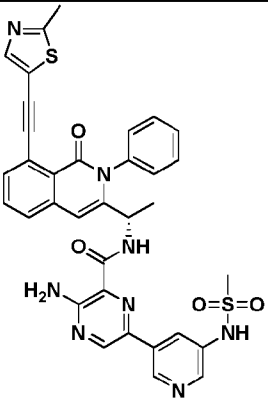
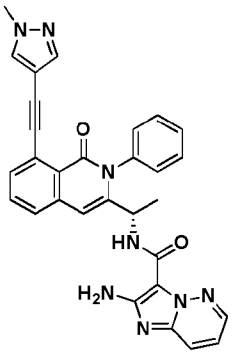
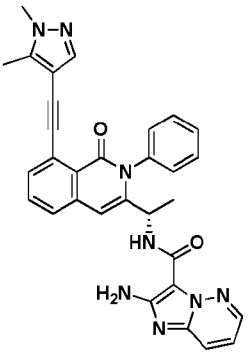
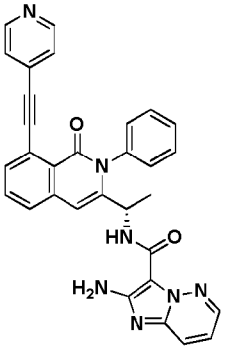
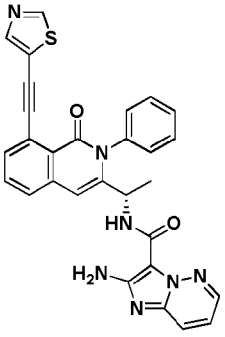
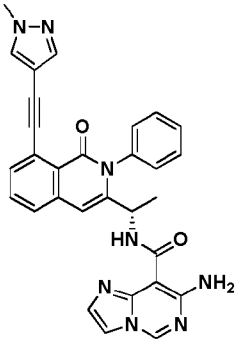
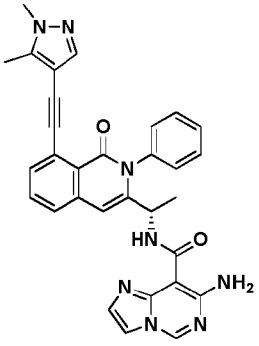
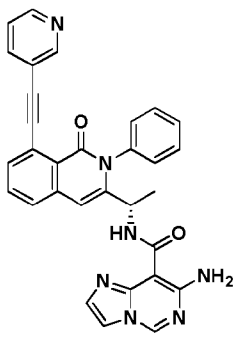
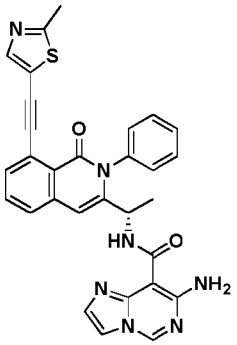
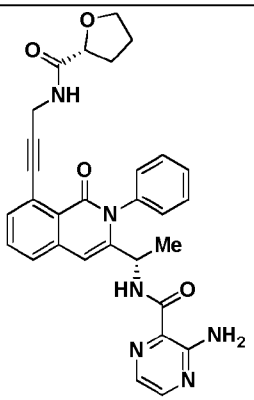
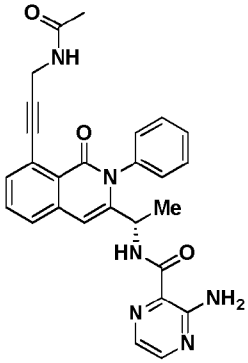
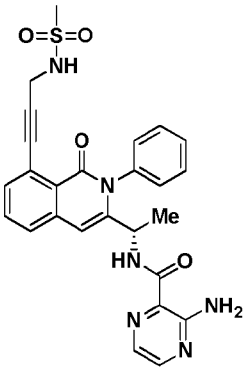
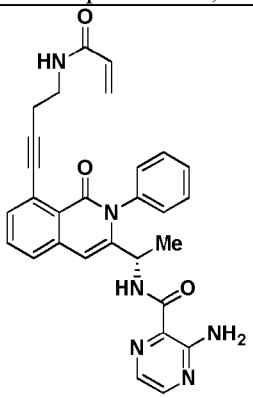
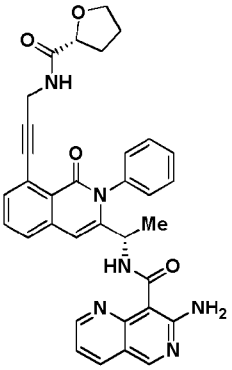
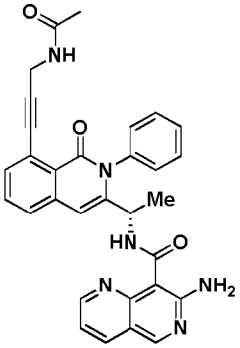
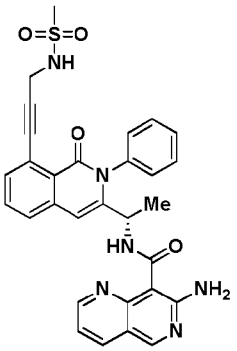
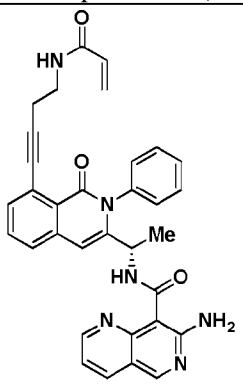
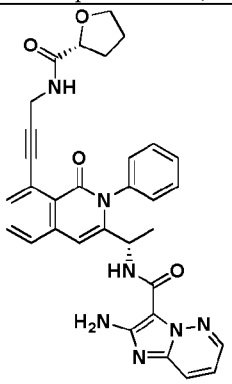
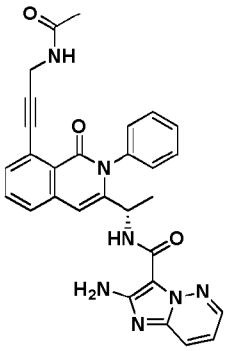
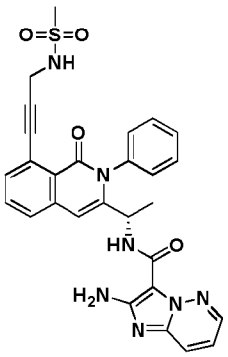
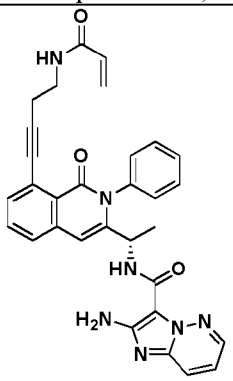
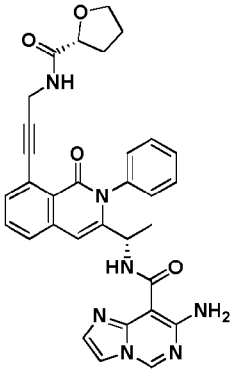
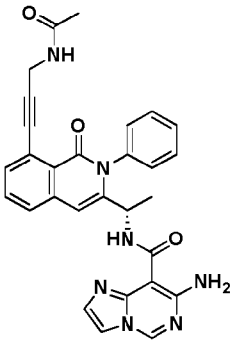
 Compound 98,	 Compound 99,	 Compound 100,	 Compound 101,
 Compound 102,	 Compound 103,	 Compound 104,	 Compound 105,
 Compound 106,	 Compound 107,	 Compound 108,	

Table 4

 Compound 1001,	 Compound 1002,	 Compound 1003,	 Compound 1004,
 Compound 1005,	 Compound 1006,	 Compound 1007,	 Compound 1008,
 Compound 1009,	 Compound 1010,	 Compound 1011,	 Compound 1012,
 Compound 1013,	 Compound 1014,	 Compound 1041,	 Compound 1042,

 Compound 1043,	 Compound 1044,	 Compound 1045,	 Compound 1046,
 Compound 1047,	 Compound 1048,	 Compound 1049,	 Compound 1050,
 Compound 1051,	 Compound 1052,	 Compound 1053,	 Compound 1054,
 Compound 1055,	 Compound 1056,	 Compound 1057,	 Compound 1058,

 Compound 1059,	 Compound 1060,	 Compound 1061,	 Compound 1062,
 Compound 1063,	 Compound 1064,	 Compound 1065,	 Compound 1066,
 Compound 1067,	 Compound 1068,	 Compound 1069,	 Compound 1070,
 Compound 1071,	 Compound 1072,	 Compound 1073,	 Compound 1074,

 Compound 1075,	 Compound 1076,	 Compound 1077,	 Compound 1078,
 Compound 1079,	 Compound 1080,	 Compound 1081,	 Compound 1082,
 Compound 1083,	 Compound 1084,	 Compound 1085,	 Compound 1086,
 Compound 1087,	 Compound 1088,	 Compound 1089,	 Compound 1090,

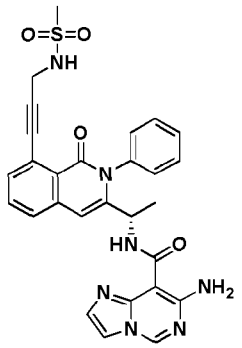
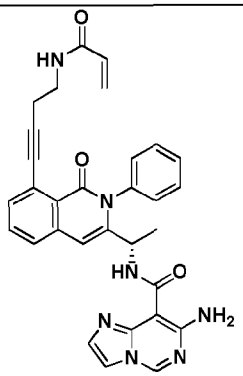
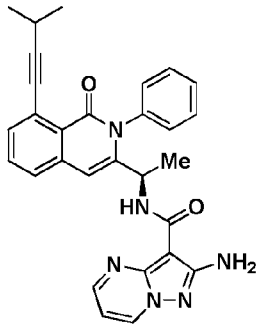
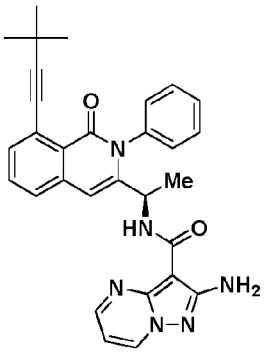
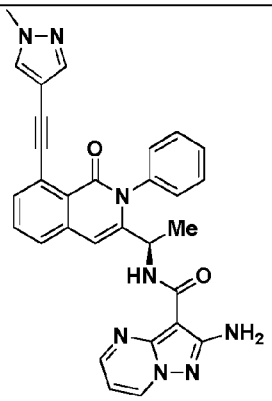
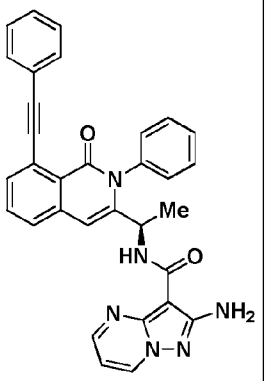
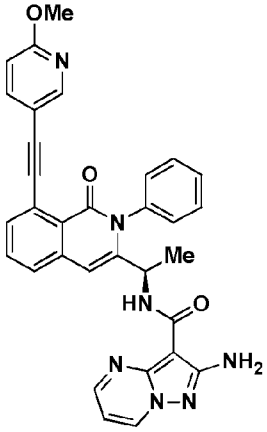
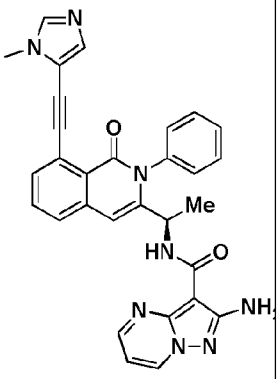
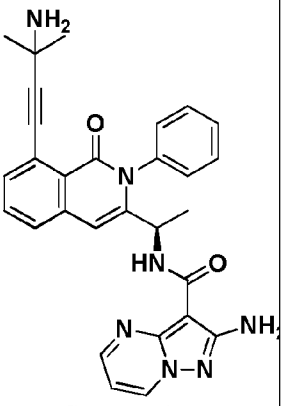
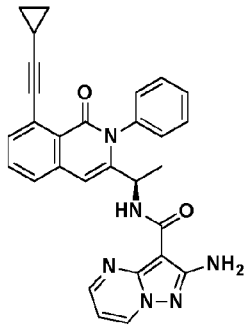
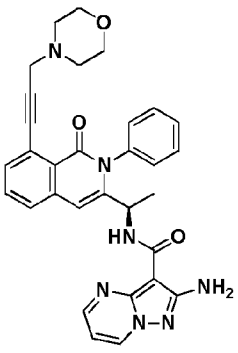
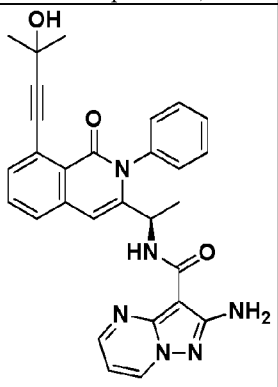
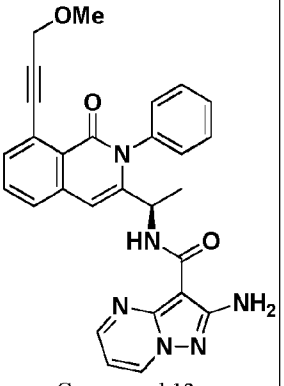
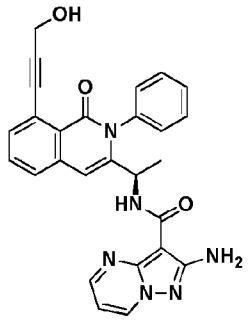
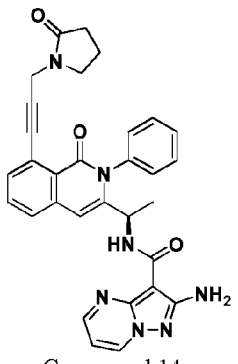
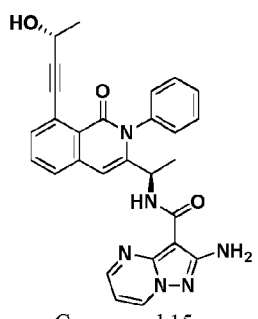
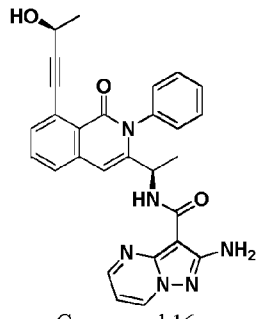
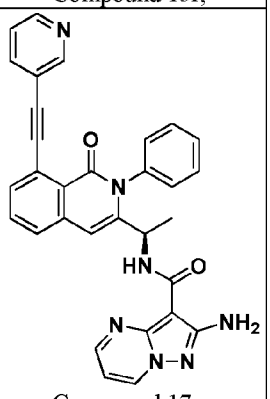
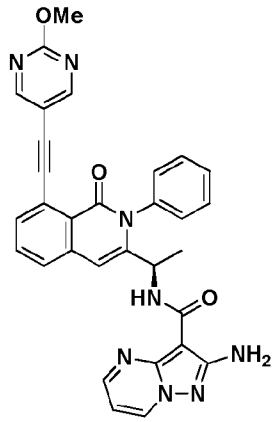
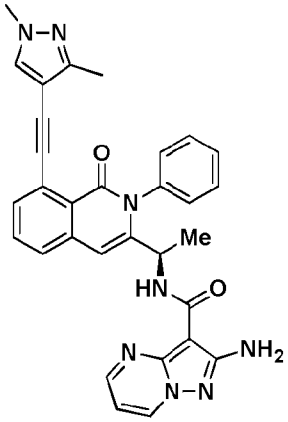
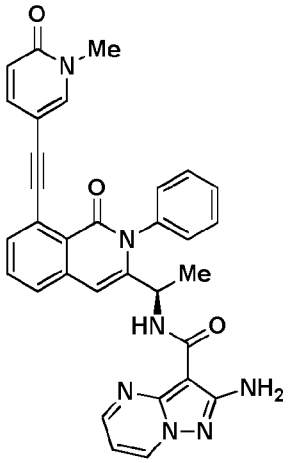
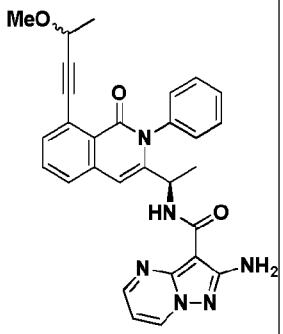
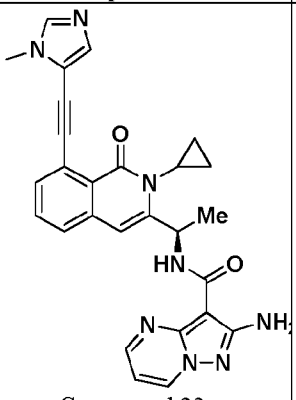
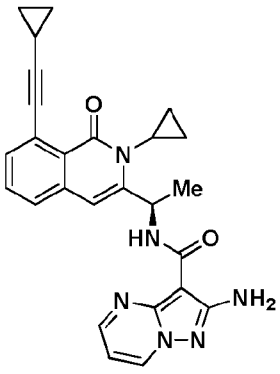
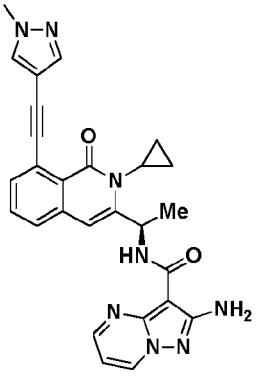
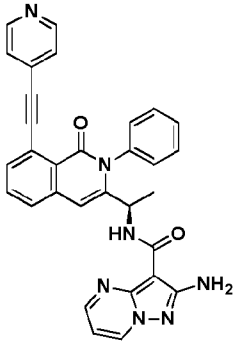
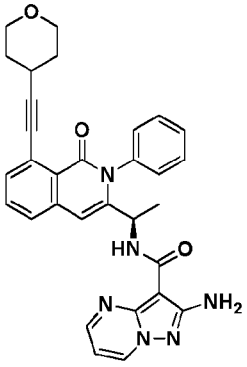
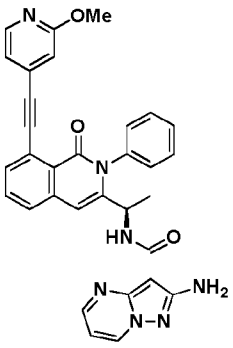
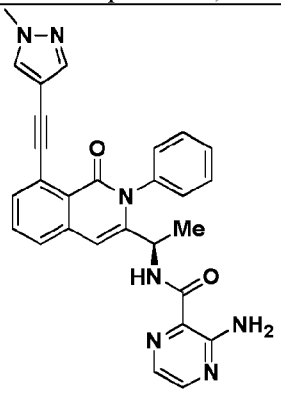
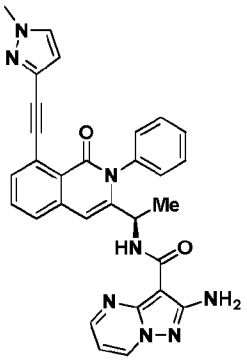
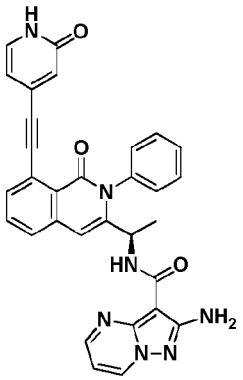
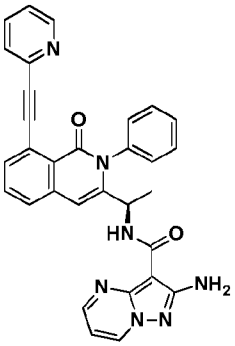
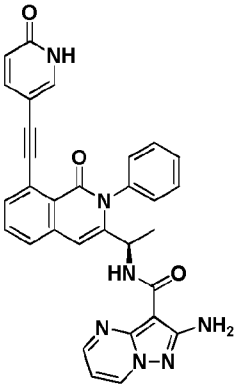
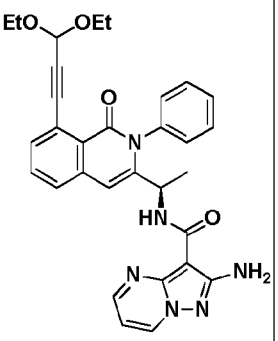
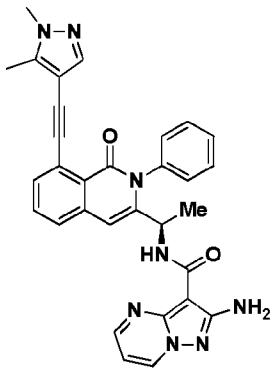
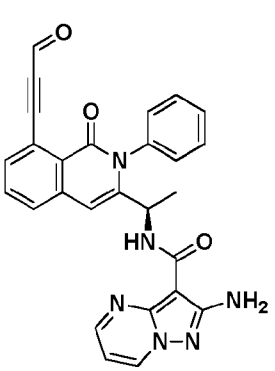
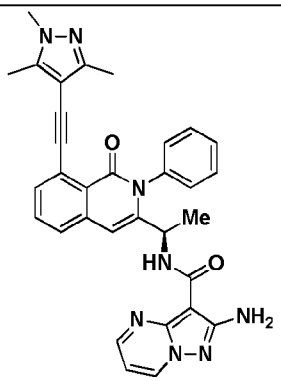
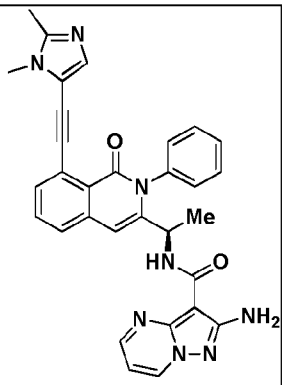
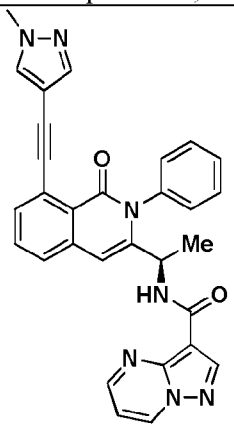
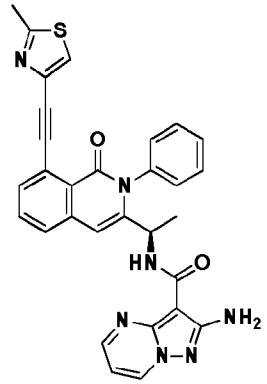
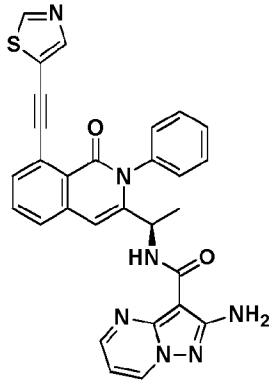
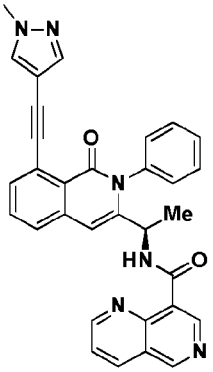
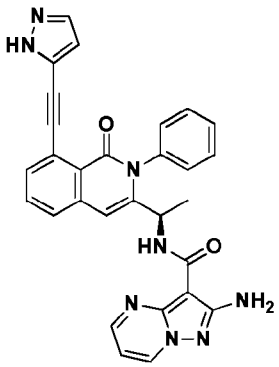
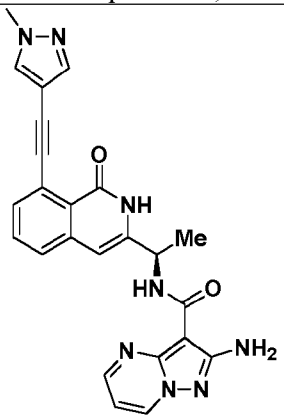
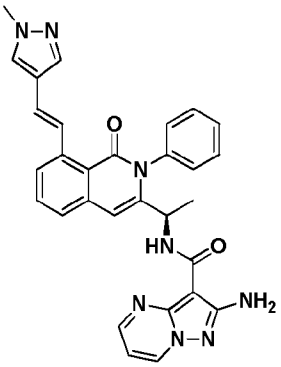
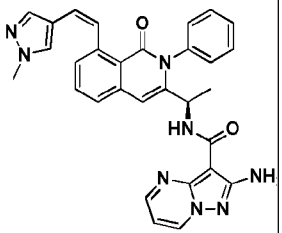
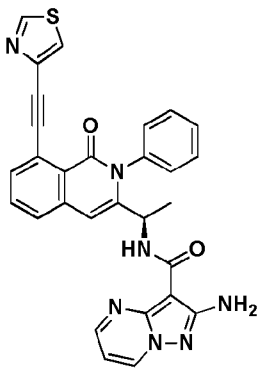
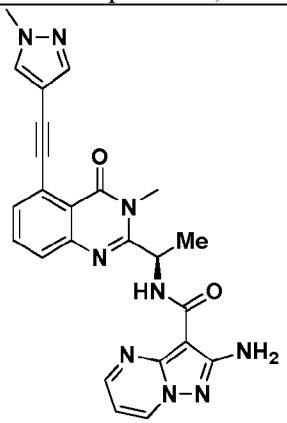
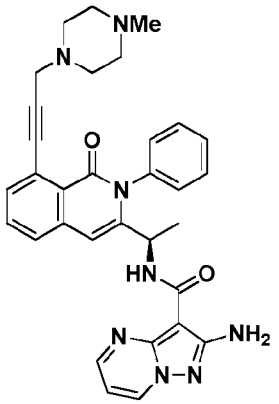
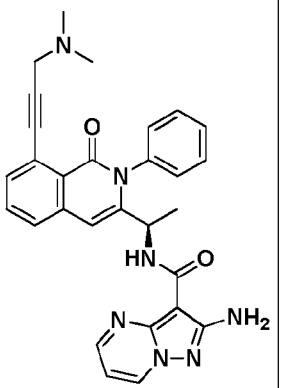
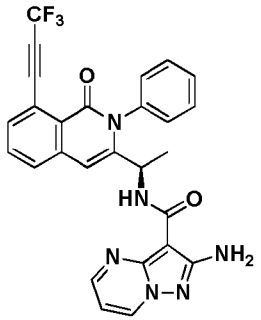
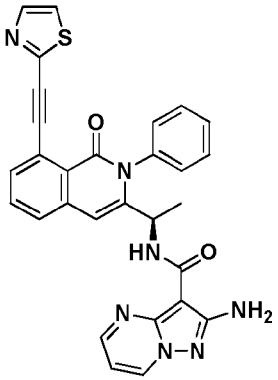
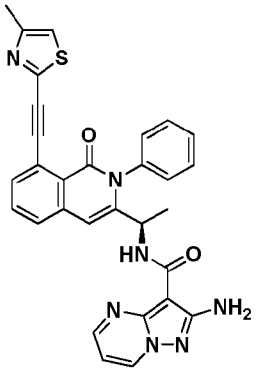
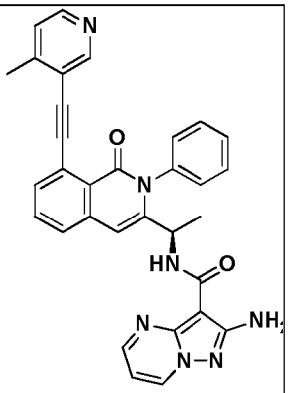
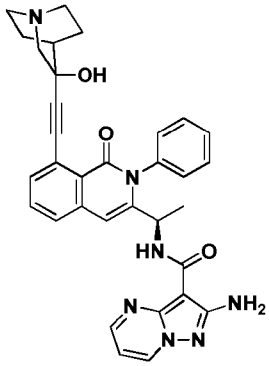
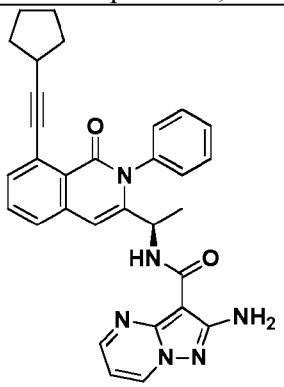
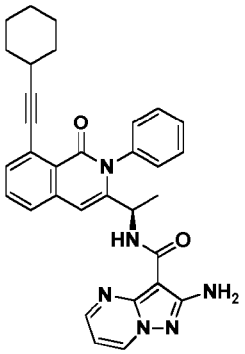
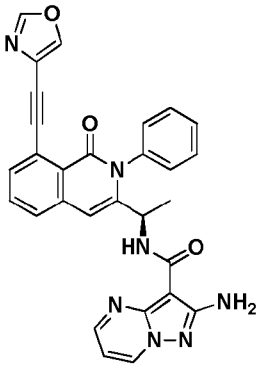
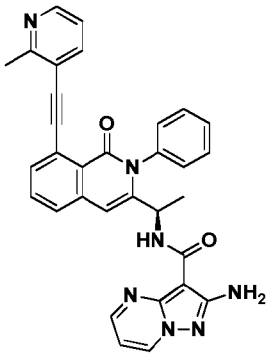
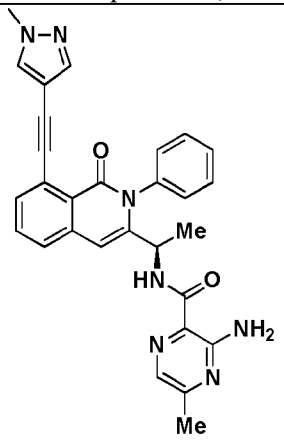
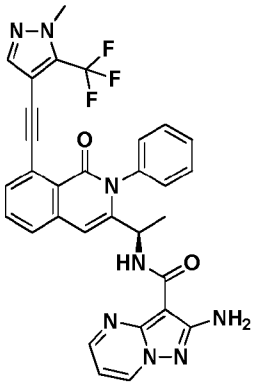
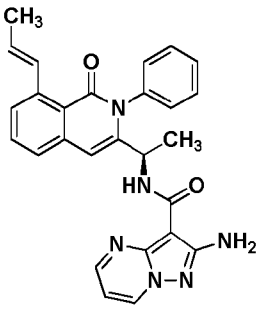
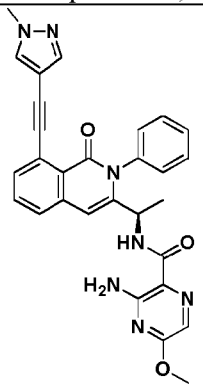
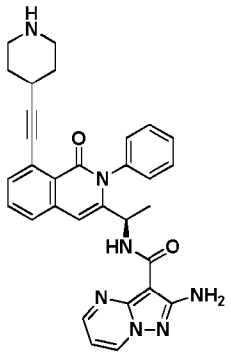
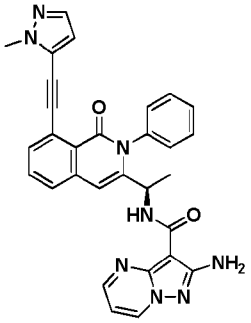
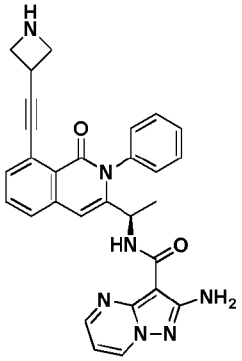
			
Compound 1091,	Compound 1092		

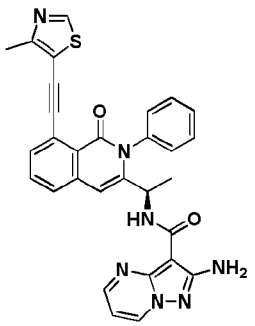
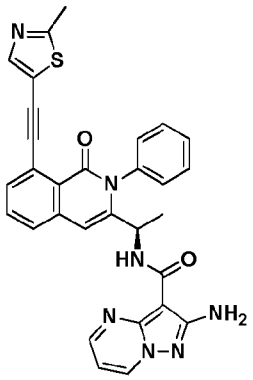
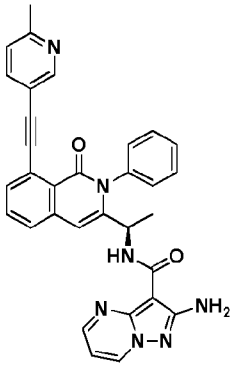
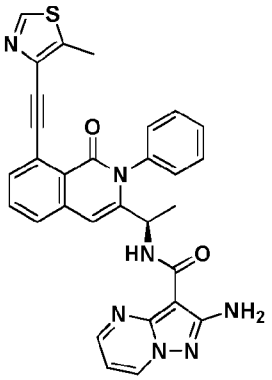
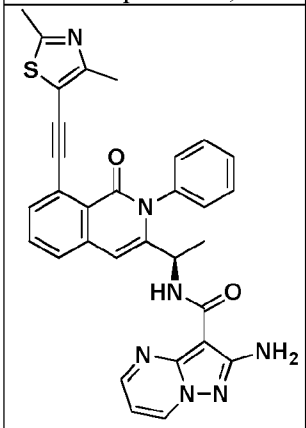
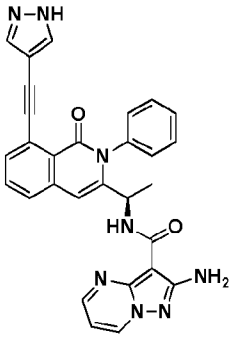
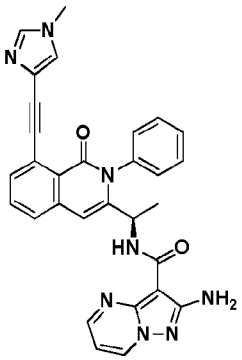
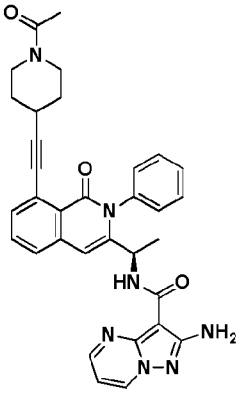
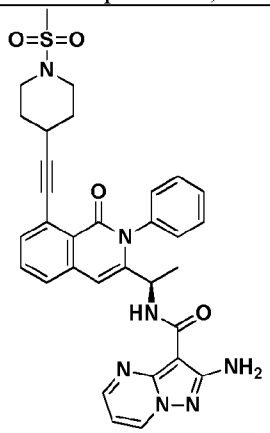
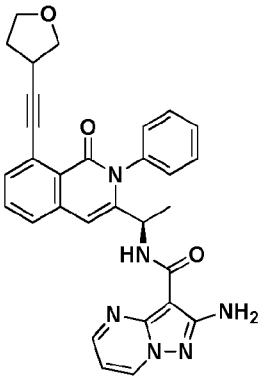
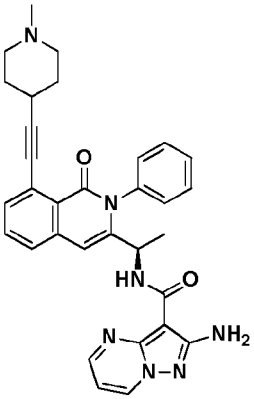
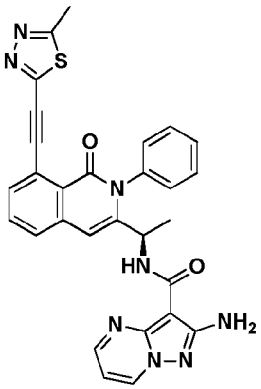
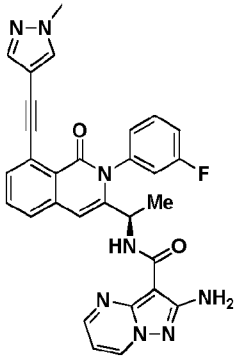
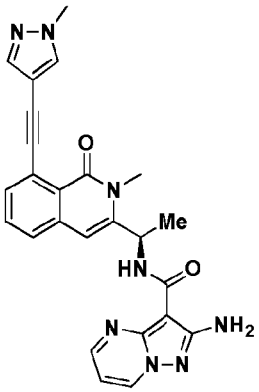
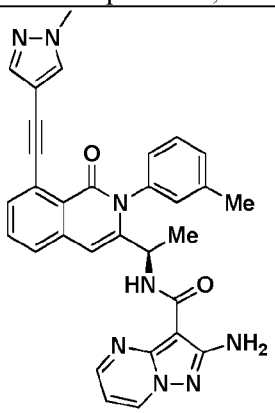
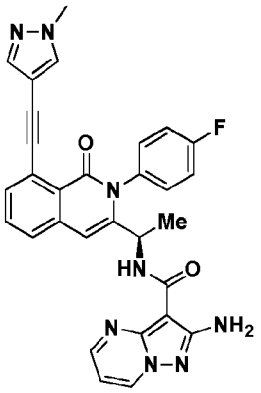
Table 11

 Compound 2r,	 Compound 3r,	 Compound 4r,	 Compound 5r,
 Compound 6r,	 Compound 7r,	 Compound 8r,	 Compound 9r,
 Compound 10r,	 Compound 11r,	 Compound 12r,	 Compound 13r,
 Compound 14r,	 Compound 15r,	 Compound 16r,	 Compound 17r,

 Compound 18r,	 Compound 19r,	 Compound 20r,	 Compound 22r,
 Compound 23r,	 Compound 24r,	 Compound 25r,	 Compound 26r,
 Compound 27r,	 Compound 28r,	 Compound 29r,	 Compound 30r,
 Compound 31r,	 Compound 32r,	 Compound 33r,	 Compound 34r,

 Compound 35r,	 Compound 36r,	 Compound 37r,	 Compound 38r,
 Compound 39r,	 Compound 40r,	 Compound 41r,	 Compound 42r,
 Compound 43r,	 Compound 44r,	 Compound 52r,	 Compound 53r,
 Compound 54r,	 Compound 55r,	 Compound 56r,	 Compound 57r,

 Compound 58r,	 Compound 59r,	 Compound 60r,	 Compound 61r,
 Compound 62r,	 Compound 64r,	 Compound 65r,	 Compound 66r,
 Compound 67r,	 Compound 68r,	 Compound 69r,	 Compound 70r,
 Compound 71r,	 Compound 72r,	 Compound 73r,	 Compound 74r,

 Compound 75r,	 Compound 76r,	 Compound 77r,	 Compound 78r,
 Compound 79r,	 Compound 80r,	 Compound 81r,	 Compound 82r,
 Compound 83r,	 Compound 84r,	 Compound 85r,	 Compound 86r,
 Compound 93r,	 Compound 94r,	 Compound 95r,	 Compound 96r,

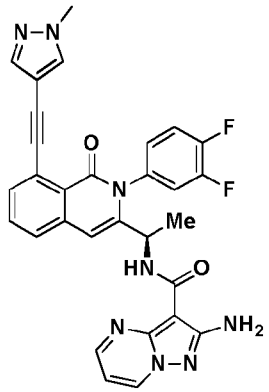
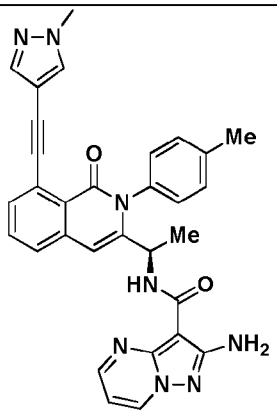
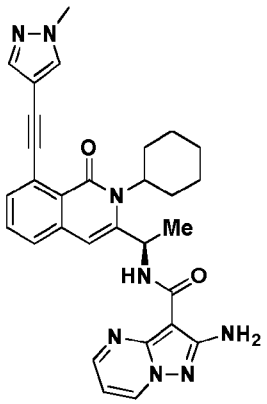
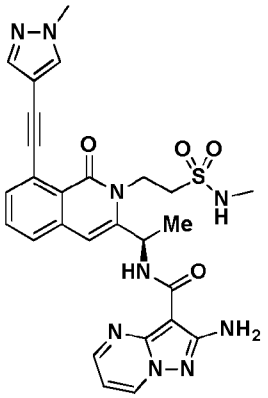
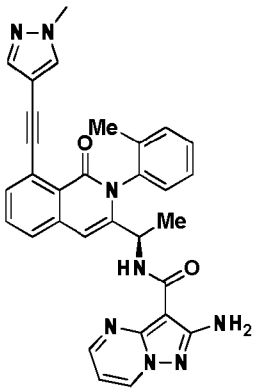
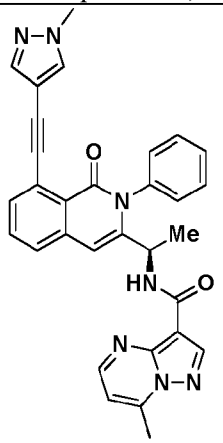
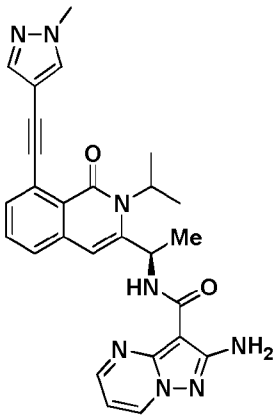
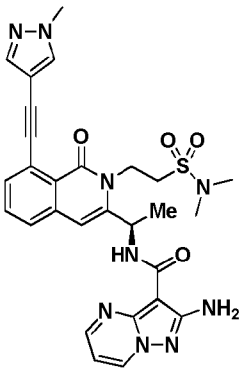
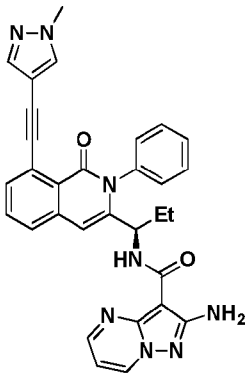
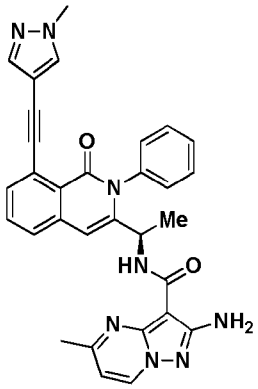
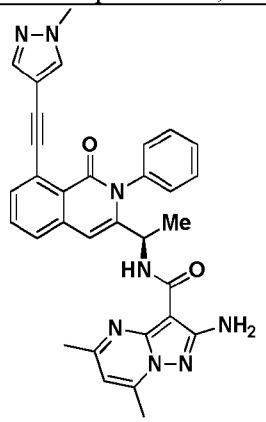
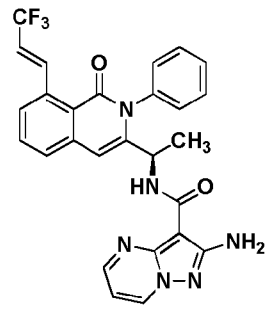
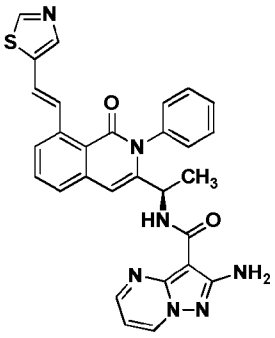
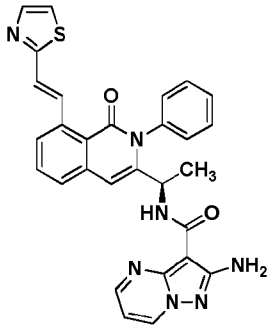
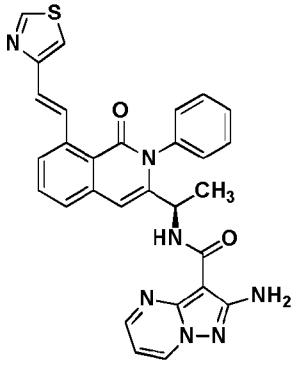
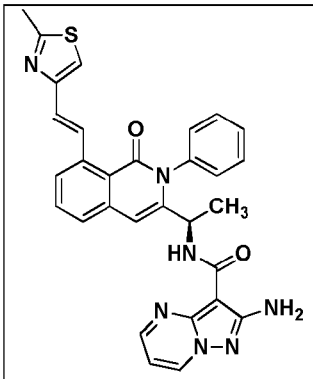
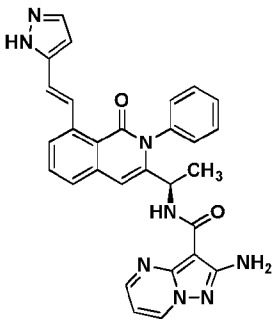
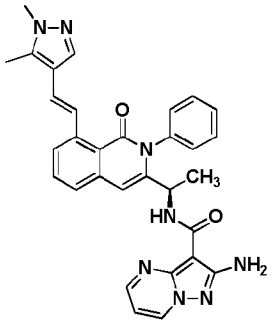
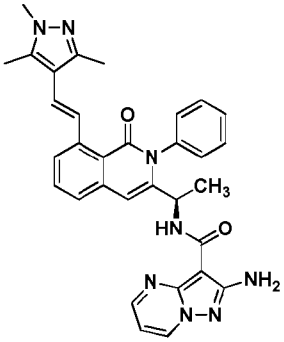
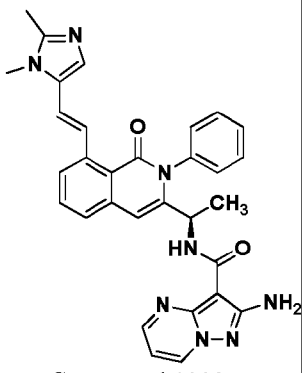
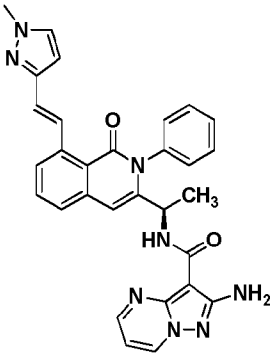
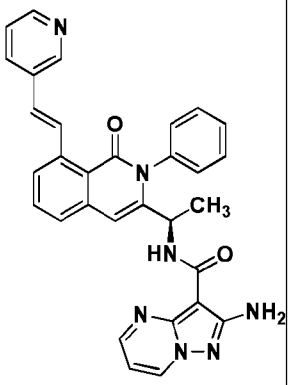
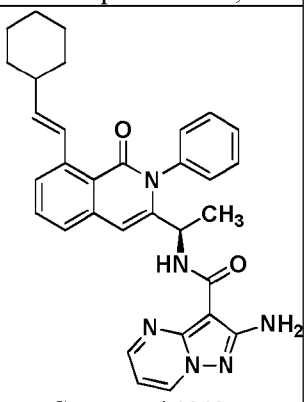
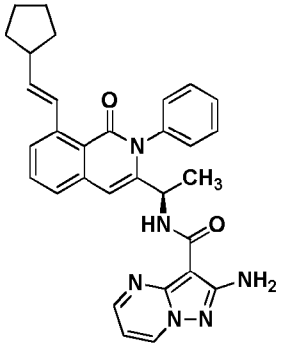
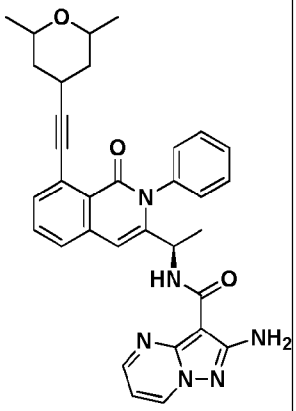
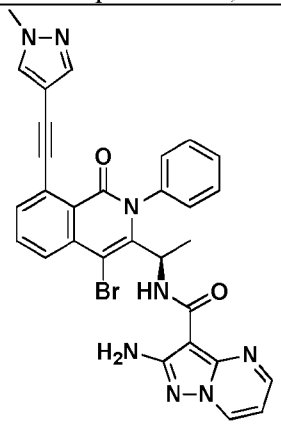
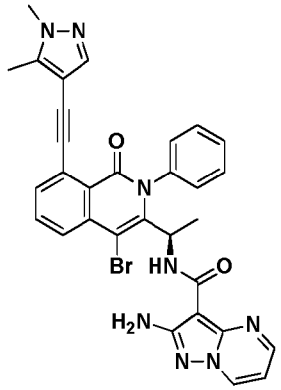
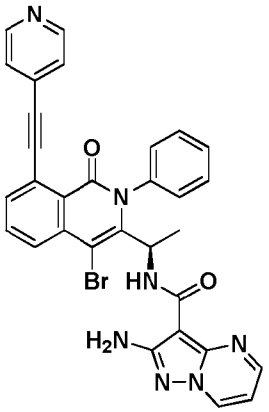
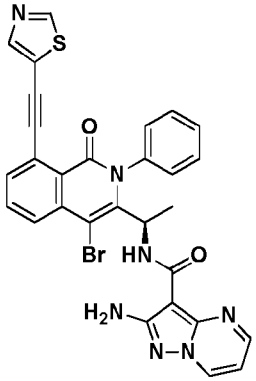
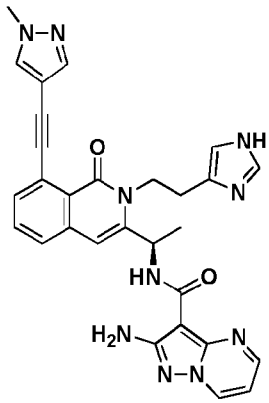
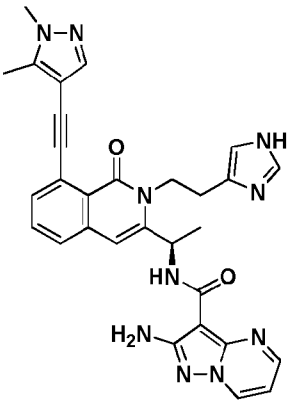
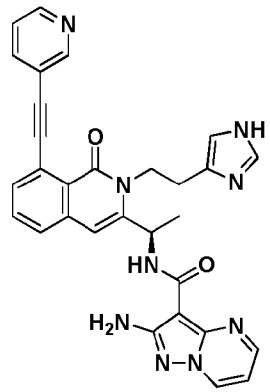
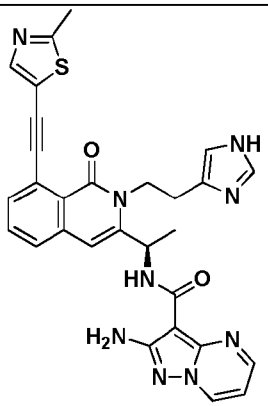
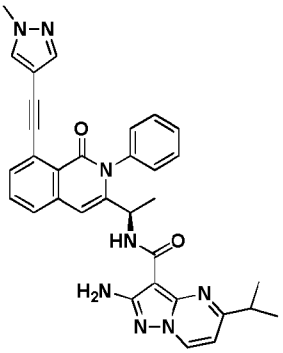
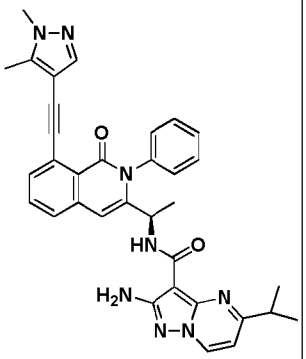
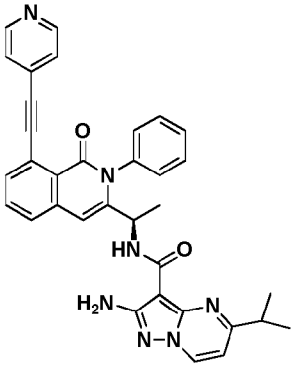
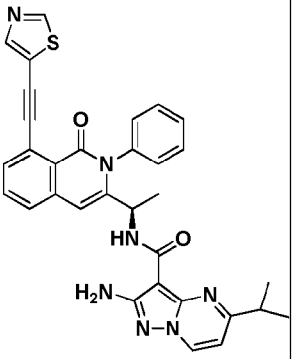
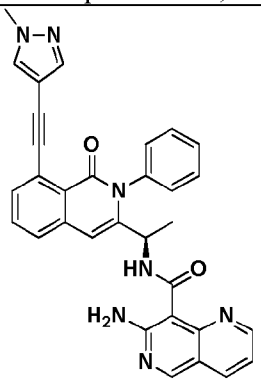
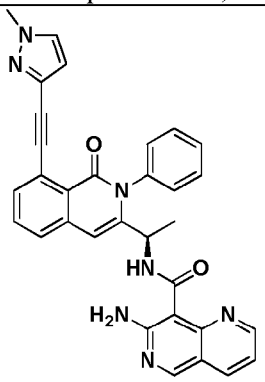
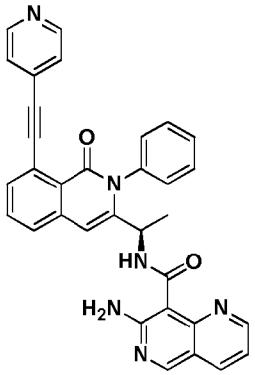
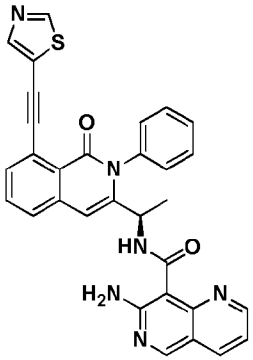
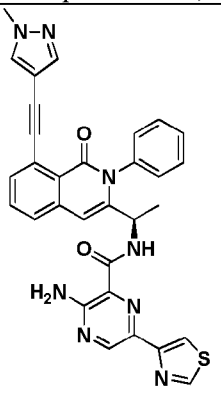
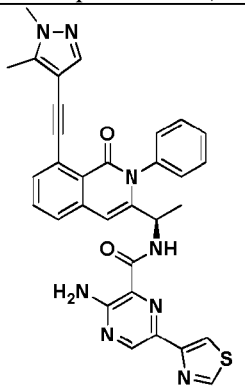
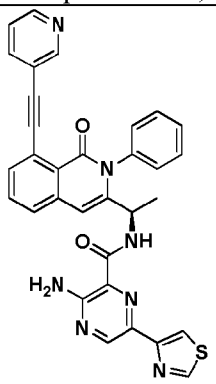
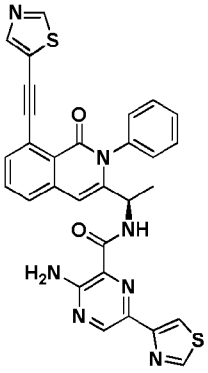
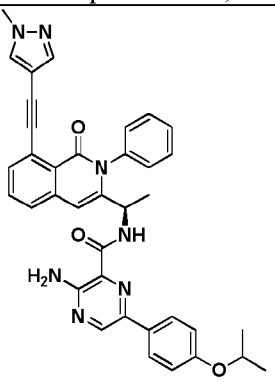
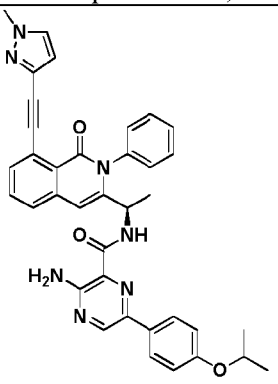
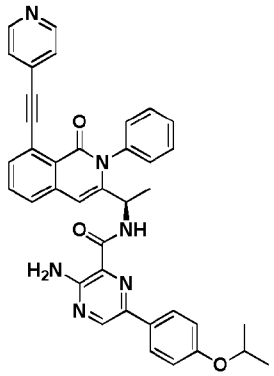
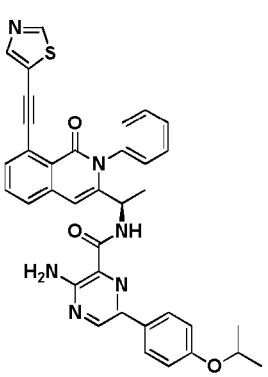
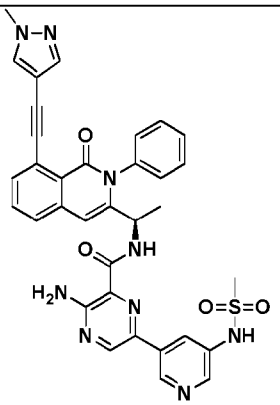
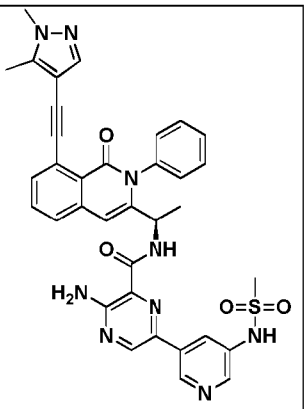
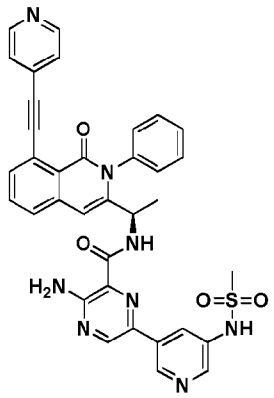
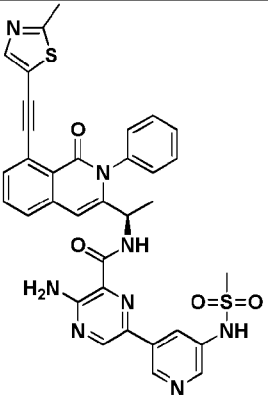
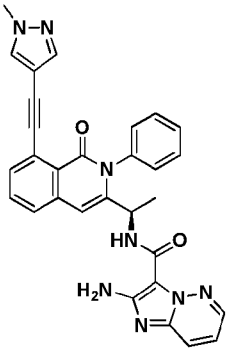
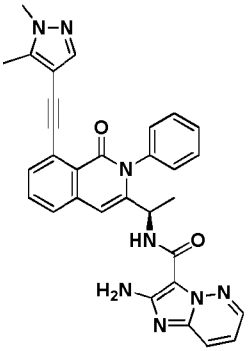
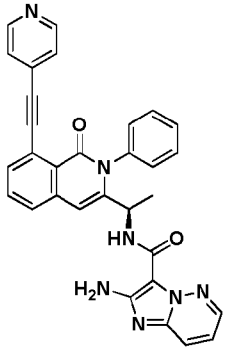
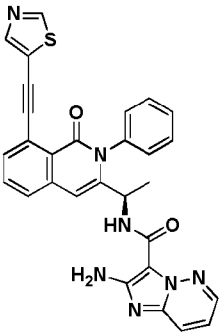
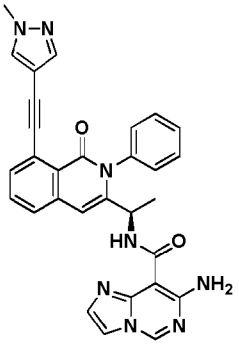
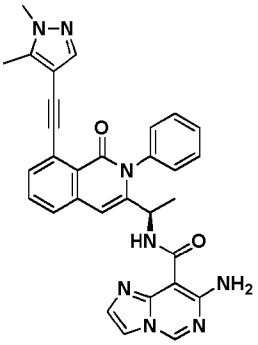
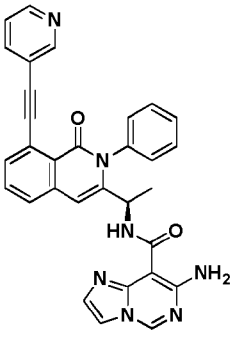
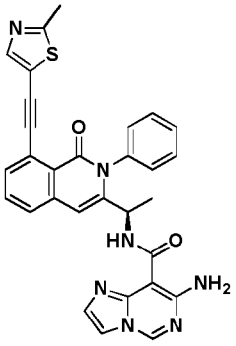
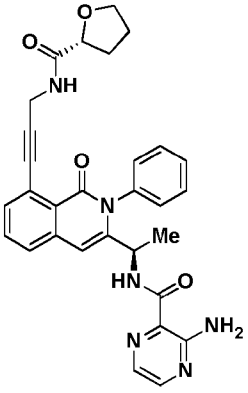
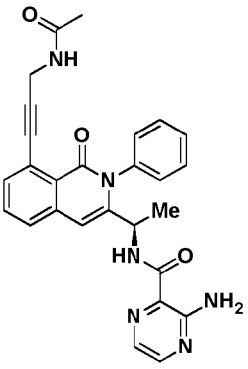
 Compound 97r,	 Compound 98r,	 Compound 99r,	 Compound 100r,
 Compound 101r,	 Compound 102r,	 Compound 103r,	 Compound 104r,
 Compound 105r,	 Compound 106r,	 Compound 108r,	

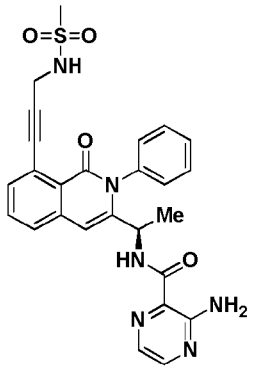
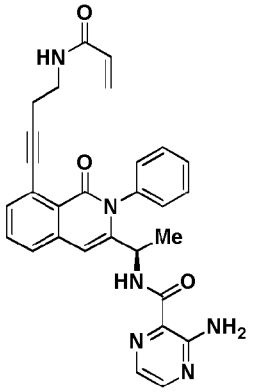
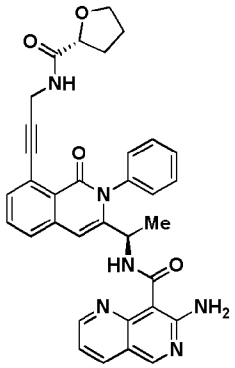
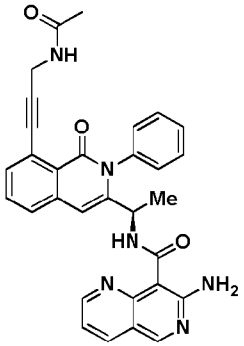
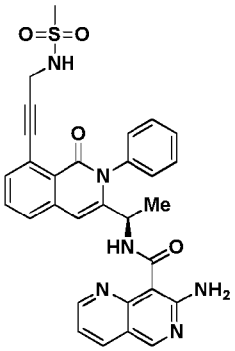
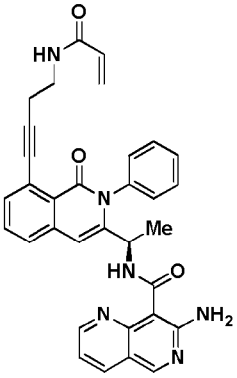
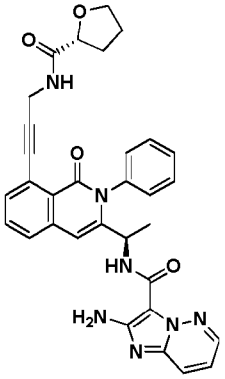
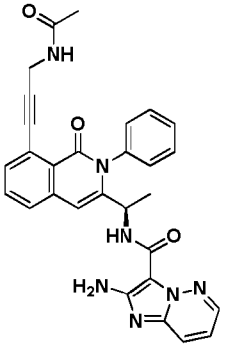
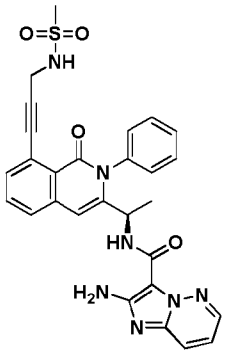
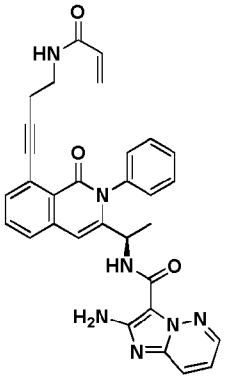
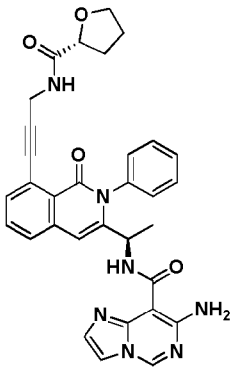
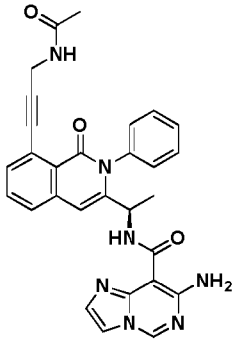
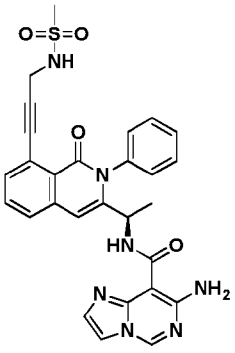
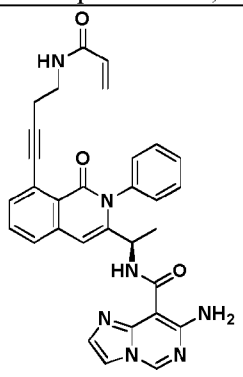
Table 12

			
Compound 1001r,	Compound 1002r,	Compound 1003r,	Compound 1004r,

 Compound 1005r,	 Compound 1006r,	 Compound 1007r,	 Compound 1008r,
 Compound 1009r,	 Compound 1010r,	 Compound 1011r,	 Compound 1012r,
 Compound 1013r,	 Compound 1014r,	 Compound 1041r,	 Compound 1042r,
 Compound 1043r,	 Compound 1044r,	 Compound 1045r,	 Compound 1046r,

 Compound 1047r,	 Compound 1048r,	 Compound 1049r,	 Compound 1050r,
 Compound 1051r,	 Compound 1052r,	 Compound 1053r,	 Compound 1054r,
 Compound 1055r,	 Compound 1056r,	 Compound 1057r,	 Compound 1058r,
 Compound 1059r,	 Compound 1060r,	 Compound 1061r,	 Compound 1062r,

 Compound 1063r,	 Compound 1064r,	 Compound 1065r,	 Compound 1066r,
 Compound 1067r,	 Compound 1068r,	 Compound 1069r,	 Compound 1070r,
 Compound 1071r,	 Compound 1072r,	 Compound 1073r,	 Compound 1074r,
 Compound 1075r,	 Compound 1076r,	 Compound 1077r,	 Compound 1078r,

 Compound 1079r,	 Compound 1080r,	 Compound 1081r,	 Compound 1082r,
 Compound 1083r,	 Compound 1084r,	 Compound 1085r,	 Compound 1086r,
 Compound 1087r,	 Compound 1088r,	 Compound 1089r,	 Compound 1090r,
 Compound 1091r,	 Compound 1092r		

Pharmaceutical Compositions

[0179] In some embodiments, provided herein are pharmaceutical compositions comprising a compound as disclosed herein, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharma-

ceutically acceptable form thereof (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers and isotopically labeled derivatives), and a pharmaceutically acceptable excipient, diluent, or carrier, including inert solid diluents and fillers, sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. In some embodiments, a pharmaceutical composition described herein includes a second active agent such as an additional therapeutic agent, *(e.g.,* a chemotherapeutic).

1. Formulations

[0180] Pharmaceutical compositions can be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (*e.g.*, those targeted for buccal, sublingual, and systemic absorption), capsules, boluses, powders, granules, pastes for application to the tongue, and intraduodenal routes; parenteral administration, including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; intravaginally or intrarectally, for example, as a pessary, cream, stent or foam; sublingually; ocularly; pulmonarily; local delivery by catheter or stent; intrathecally, or nasally.

[0181] Examples of suitable aqueous and nonaqueous carriers which can be employed in pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0182] These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents, dispersing agents, lubricants, and/or antioxidants. Prevention of the action of microorganisms upon the compounds described herein can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It can also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0183] Methods of preparing these formulations or compositions include the step of bringing into association a compound described herein and/or the chemotherapeutic with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound as disclosed herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0184] 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; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., Basic and Clinical Pharmacology, Twelfth Edition, McGraw Hill, 2011; Goodman and Gilman, eds., The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001; Remingtons Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The Pharmaceutical Press, London, 1999). Except insofar as any conventional excipient medium is incompatible with the compounds provided herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, the excipient's use is contemplated to be within the scope of this disclosure.

[0185] In some embodiments, the concentration of one or more of the compounds provided in the disclosed pharmaceutical compositions is less than about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about 0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001%, w/w, w/v or v/v.

[0186] In some embodiments, the concentration of one or more of the compounds as disclosed herein is greater than about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19.75%, about 19.50%, about 19.25%, about 19%, about 18.75%, about 18.50%, about 18.25%, about 18%, about 17.75%, about 17.50%, about 17.25%, about 17%, about 16.75%, about 16.50%, about 16.25%, about 16%, about 15.75%, about 15.50%, about 15.25%, about 15%, about 14.75%, about 14.50%, about 14.25%, about 14%, about 13.75%, about 13.50%, about 13.25%, about 13%, about 12.75%, about 12.50%, about 12.25%, about 12%, about 11.75%, about 11.50%, about 11.25%, about 11%, about 10.75%, about 10.50%, about 10.25%, about 10%, about 9.75%, about 9.50%, about 9.25%, about 9%, about 8.75%, about 8.50%, about 8.25%, about 8%, about 7.75%, about 7.50%, about 7.25%,

about 7%, about 6.75%, about 6.50%, about 6.25%, about 6%, about 5.75%, about 5.50%, about 5.25%, about 5%, about 4.75%, about 4.50%, about 4.25%, about 4%, about 3.75%, about 3.50%, about 3.25%, about 3%, about 2.75%, about 2.50%, about 2.25%, about 2%, about 1.75%, about 1.50%, about 1.25%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about 0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001%, w/w, w/v, or v/v.

[0187] In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, or approximately 1% to approximately 10%, w/w, w/v or v/v.

[0188] In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, or approximately 0.1% to approximately 0.9%, w/w, w/v or v/v.

[0189] In some embodiments, the amount of one or more of the compounds as disclosed herein is equal to or less than about 10 g, about 9.5 g, about 9.0 g, about 8.5 g, about 8.0 g, about 7.5 g, about 7.0 g, about 6.5 g, about 6.0 g, about 5.5 g, about 5.0 g, about 4.5 g, about 4.0 g, about 3.5 g, about 3.0 g, about 2.5 g, about 2.0 g, about 1.5 g, about 1.0 g, about 0.95 g, about 0.9 g, about 0.85 g, about 0.8 g, about 0.75 g, about 0.7 g, about 0.65 g, about 0.6 g, about 0.55 g, about 0.5 g, about 0.45 g, about 0.4 g, about 0.35 g, about 0.3 g, about 0.25 g, about 0.2 g, about 0.15 g, about 0.1 g, about 0.09 g, about 0.08 g, about 0.07 g, about 0.06 g, about 0.05 g, about 0.04 g, about 0.03 g, about 0.02 g, about 0.01 g, about 0.009 g, about 0.008 g, about 0.007 g, about 0.006 g, about 0.005 g, about 0.004 g, about 0.003 g, about 0.002 g, about 0.001 g, about 0.0009 g, about 0.0008 g, about 0.0007 g, about 0.0006 g, about 0.0005 g, about 0.0004 g, about 0.0003 g, about 0.0002 g, or about 0.0001 g.

[0190] In some embodiments, the amount of one or more of the compounds as disclosed herein is more than about 0.0001 g, about 0.0002 g, about 0.0003 g, about 0.0004 g, about 0.0005 g, about 0.0006 g, about 0.0007 g, about 0.0008 g, about 0.0009 g, about 0.001 g, about 0.0015 g, about 0.002 g, about 0.0025 g, about 0.003 g, about 0.0035 g, about 0.004 g, about 0.0045 g, about 0.005 g, about 0.0055 g, about 0.006 g, about 0.0065 g, about 0.007 g, about 0.0075 g, about 0.008 g, about 0.0085 g, about 0.009 g, about 0.0095 g, about 0.01 g, about 0.015 g, about 0.02 g, about 0.025 g, about 0.03 g, about 0.035 g, about 0.04 g, about 0.045 g, about 0.05 g, about 0.055 g, about 0.06 g, about 0.065 g, about 0.07 g, about 0.075 g, about 0.08 g, about 0.085 g, about 0.09 g, about 0.095 g, about 0.1 g, about 0.15 g, about 0.2 g, about 0.25 g, about 0.3 g, about 0.35 g, about 0.4 g, about 0.45 g, about 0.5 g, about 0.55 g, about 0.6 g, about 0.65 g, about 0.7 g, about 0.75 g, about 0.8 g, about 0.85 g, about 0.9 g, about 0.95 g, about 1 g, about 1.5 g, about 2 g, about 2.5 g, about 3 g, about 3.5 g, about 4 g, about 4.5 g, about 5 g, about 5.5 g, about 6 g, about 6.5 g, about 7 g, about 7.5 g, about 8 g, about 8.5 g, about 9 g, about 9.5 g, or about 10 g.

[0191] In some embodiments, the amount of one or more of the compounds as disclosed herein is in the range of about 0.0001 to about 10 g, about 0.0005 to about 9 g, about 0.001 to about 8 g, about 0.005 to about 7 g, about 0.01 to about 6 g, about 0.05 to about 5 g, about 0.1 to about 4 g, about 0.5 to about 4 g, or about 1 to about 3 g.

1A. Formulations for oral administration

[0192] In some embodiments, provided herein are pharmaceutical compositions for oral administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for oral administration. In some embodiments, provided herein are pharmaceutical compositions for oral administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for oral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[0193] In some embodiments, the pharmaceutical composition can be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions 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 into association with the carrier, which constitutes one or more ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately admixing the active ingredient 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.

[0194] The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (*e.g.*, about 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 can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms 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 can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can 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.

[0195] An active ingredient 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 pharmaceutical 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. In some embodiments, tablets can be coated by standard aqueous or nonaqueous techniques.

[0196] 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.

[0197] 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.

[0198] Disintegrants can be used in the pharmaceutical compositions as provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant can produce tablets which can disintegrate in the bottle. Too little can be insufficient for disintegration to occur and can thus alter the rate and extent of release of the active ingredient(s) 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) can be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used can vary based upon the type of formulation and mode of administration, and can 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, can be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms 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.

[0199] Lubricants which can be used to form pharmaceutical compositions and dosage forms 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.

[0200] When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient therein can be combined with various sweetening or flavoring agents, coloring matter or dyes and, for example, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[0201] 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.

[0202] Surfactant which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants can be employed, a mixture of lipophilic surfactants can be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant can be employed.

[0203] A suitable hydrophilic surfactant can generally have an HLB value of at least about 10, while suitable lipophilic surfactants can 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.

[0204] Hydrophilic surfactants can 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.

[0205] 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.

[0206] Ionic surfactants can 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.

[0207] Hydrophilic non-ionic surfactants can include, but are 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 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 triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol can be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[0208] 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-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[0209] 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 glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, non-limiting examples of 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 vegetable oils, hydrogenated vegetable oils, and triglycerides.

[0210] In one embodiment, the pharmaceutical composition can include a solubilizer to ensure good solubilization and/or dissolution of a compound as provided herein and to minimize precipitation of the compound. This can be especially important for pharmaceutical compositions for non-oral use, *e.g.*, pharmaceutical compositions for injection. A solubilizer can also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the pharmaceutical composition as a stable or homogeneous solution or dispersion.

[0211] 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, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-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.

[0212] Mixtures of solubilizers can 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. In some embodiments, solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[0213] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer can be limited to a bioacceptable amount, which can be readily determined by one of skill in the art. In some circumstances, it can 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 pharmaceutical composition to a subject using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of about 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 can also be used, such as about 5%, 2%, 1% or even less. Typically, the solubilizer can be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[0214] The pharmaceutical 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, oils, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[0215] Exemplary preservatives can include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium

edetate, tartaric acid, and trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

[0216] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[0217] In addition, an acid or a base can be incorporated into the pharmaceutical 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, alkaline earth metals, and the like. Examples can include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[0218] 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, uric acid and the like.

1B. Formulations for Parenteral Administration

[0219] In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for parenteral administration. In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for parenteral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[0220] The forms in which the disclosed pharmaceutical compositions can 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.

[0221] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid

polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed.

[0222] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can 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, thimerosal, and the like.

[0223] Sterile injectable solutions are prepared by incorporating a compound as disclosed herein in the required amount in the appropriate solvent with various other ingredients as enumerated above, as appropriate, 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 appropriate other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional ingredient from a previously sterile-filtered solution thereof.

[0224] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. Injectable compositions can contain from about 0.1 to about 5% w/w of a compound as disclosed herein.

1C. Formulations for Topical Administration

[0225] In some embodiments, provided herein are pharmaceutical compositions for topical (e.g., transdermal) administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for topical administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for topical administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[0226] Pharmaceutical compositions provided herein 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 can provide more immediate exposure of the active ingredient to the chosen area.

[0227] The pharmaceutical compositions also can 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.

[0228] Another exemplary formulation for use in the disclosed methods employs transdermal delivery devices ("patches"). Such transdermal patches can be used to provide continuous or discontinuous infusion of a compound as provided herein in controlled amounts, either with or without another agent.

[0229] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.,* U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches can be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0230] Suitable devices for use in delivering intradermal pharmaceutically acceptable compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers

of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[0231] Topically-administrable formulations can, for example, comprise from about 1% to about 10% (w/w) of a compound provided herein relative to the total weight of the formulation, although the concentration of the compound provided herein in the formulation can be as high as the solubility limit of the compound in the solvent. In some embodiments, topically-administrable formulations can, for example, comprise from about 1% to about 9% (w/w) of a compound provided herein, such as from about 1% to about 8% (w/w), further such as from about 1% to about 7% (w/w), further such as from about 1% to about 6% (w/w), further such as from about 1% to about 5% (w/w), further such as from about 1% to about 4% (w/w), further such as from about 1% to about 3% (w/w), and further such as from about 1% to about 2% (w/w) of a compound provided herein. Formulations for topical administration can further comprise one or more of the additional pharmaceutically acceptable excipients described herein.

1D. Formulations for Inhalation Administration

[0232] In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for inhalation administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[0233] Pharmaceutical 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 pharmaceutical compositions can contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the pharmaceutical compositions are administered by the oral or nasal respiratory route for local or systemic effect. Pharmaceutical compositions in pharmaceutically acceptable solvents can be nebulized by use of inert gases. Nebulized solutions can be inhaled directly from the nebulizing device or the nebulizing device can be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder pharmaceutical compositions can be administered, *e.g.*, orally or nasally, from devices that deliver the formulation in an appropriate manner.

1E. Formulations for Ocular Administration

[0234] In some embodiments, the disclosure provides a pharmaceutical composition for treating ophthalmic disorders. The pharmaceutical composition can contain an effective amount of a compound as disclosed herein and a pharmaceutical excipient suitable for ocular administration. Pharmaceutical compositions suitable for ocular administration can be presented as discrete dosage forms, such as drops or sprays each containing a predetermined amount of an active ingredient a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Other administration foms include intraocular injection, intravitreal injection, topically, or through the use of a drug eluting device, microcapsule, implant, or microfluidic device. In some cases, the compounds as disclosed herein are administered with a carrier or excipient that increases the intraocular penetrance of the compound such as an oil and water emulsion with colloid particles having an oily core surrounded by an interfacial film. It is contemplated that all local routes to the eye can be used including topical, subconjunctival, periocular, retrobulbar, subtenon, intracameral, intravitreal, intraocular, subretinal, juxtascleral and suprachoroidal administration. Systemic or parenteral administration can be feasible including, but not limited to intravenous, subcutaneous, and oral delivery. An exemplary method of administration will be intravitreal or subtenon injection of solutions or suspensions, or intravitreal or subtenon placement of bioerodible or non-bioerodible devices, or by topical ocular administration of solutions or suspensions, or posterior juxtascleral administration of a gel or cream formulation.

[0235] Eye drops can be prepared by dissolving the active ingredient in a sterile aqueous solution such as physiological saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. Other vehicles can be chosen, as is known in the art, including, but not limited to: balance salt solution, saline solution, water soluble polyethers such as polyethyene glycol, polyvinyls, such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate. In some embodiments, additives ordinarily used in the eye drops can be added. Such additives include isotonizing agents (*e.g.,* sodium chloride, etc.), buffer agent (*e.g.,* boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (*e.g.*, benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (*e.g.,* saccharide such as lactose, mannitol, maltose, etc.; *e.g.,* hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; *e.g.,* mucopolysaccharide such as chondroitin sulfate, etc.; *e.g.,* sodium polyacrylate, carboxyvinyl polymer, crosslinked poly-

acrylate, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art).

[0236] In some cases, the colloid particles include at least one cationic agent and at least one non-ionic sufactant such as a poloxamer, tyloxapol, a polysorbate, a polyoxyethylene castor oil derivative, a sorbitan ester, or a polyoxyl stearate. In some cases, the cationic agent is an alkylamine, a tertiary alkyl amine, a quarternary ammonium compound, a cationic lipid, an amino alcohol, a biguanidine salt, a cationic compound or a mixture thereof. In some cases, the cationic agent is a biguanidine salt such as chlorhexidine, polyaminopropyl biguanidine, phenformin, alkylbiguanidine, or a mixture thereof. In some cases, the quaternary ammonium compound is a benzalkonium halide, lauralkonium halide, cetrimide, hexadecyltrimethylammonium halide, tetradecyltrimethylammonium halide, dodecyltrimethylammonium halide, cetrimonium halide, benzethonium halide, behenalkonium halide, cetalkonium halide, cetethyldimonium halide, cetylpyridinium halide, benzododecinium halide, chlorallyl methenamine halide, rnyristylalkonium halide, stearalkonium halide or a mixture of two or more thereof. In some cases, cationic agent is a benzalkonium chloride, lauralkonium chloride, benzododecinium bromide, benzethenium chloride, hexadecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide or a mixture of two or more thereof. In some cases, the oil phase is mineral oil and light mineral oil, medium chain triglycerides (MCT), coconut oil; hydrogenated oils comprising hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenate castor oil or hydrogenated soybean oil; polyoxyethylene hydrogenated castor oil derivatives comprising poluoxyl-40 hydrogenated castor oil, polyoxyl-60 hydrogenated castor oil or polyoxyl-100 hydrogenated castor oil.

1F. Formulations for Controlled Release Administration

[0237] In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for controlled release administration. In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for controlled release administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[0238] Active agents such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,699,500. Such dosage forms can be used to provide slow or controlled release of one or more active agents using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active agents provided herein. Thus, the pharmaceutical compositions provided encompass single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled release.

[0239] All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non controlled counterparts. In some embodiments, the use of a controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the disease, disorder, or condition in a minimum amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

[0240] In some embodiments, controlled release formulations are designed to initially release an amount of a compound as disclosed herein that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of the compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of the compound in the body, the compound should be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active agent can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[0241] In certain embodiments, the pharmaceutical composition can be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump can be used (*see,* Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et αl., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner

of skill, *e.g.,* thus requiring only a fraction of the systemic dose (*see, e.g.,* Goodson, Medical Applications of Controlled Release, 115-138 (vol. 2, 1984). Other controlled release systems are discussed in the review by Langer, Science 249:1527-1533 (1990). The one or more active agents can be dispersed in a solid inner matrix, *e.g.,* polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The one or more active agents then diffuse through the outer polymeric membrane in a release rate controlling step. The percentage of active agent in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

2. Dosage

[0242] A compound described herein can be delivered in the form of pharmaceutically acceptable compositions which comprise a therapeutically effective amount of one or more compounds described herein and/or one or more additional therapeutic agents such as a chemotherapeutic, formulated together with one or more pharmaceutically acceptable excipients. In some instances, the compound described herein and the additional therapeutic agent are administered in separate pharmaceutical compositions and can *(e.g.,* because of different physical and/or chemical characteristics) be administered by different routes (*e.g.*, one therapeutic is administered orally, while the other is administered intravenously). In other instances, the compound described herein and the additional therapeutic agent can be administered separately, but via the same route (*e.g.*, both orally or both intravenously). In still other instances, the compound described herein and the additional therapeutic agent can be administered in the same pharmaceutical composition.

[0243] The selected dosage level will depend upon a variety of factors including, for example, the activity of the particular compound employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0244] In general, a suitable daily dose of a compound described herein and/or a chemotherapeutic will be that amount of the compound which, in some embodiments, can be the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described herein. Generally, doses of the compounds described herein for a patient, when used for the indicated effects, will range from about 0.0001 mg to about 100 mg per day, or about 0.001 mg to about 100 mg per day, or about 0.01 mg to about 100 mg per day, or about 0.1 mg to about 100 mg per day, or about 0.0001 mg to about 500 mg per day, or about 0.001 mg to about 500 mg per day, or about 0.01 mg to 1000 mg, or about 0.01 mg to about 500 mg per day, or about 0.1 mg to about 500 mg per day, or about 1 mg to 50 mg per day, or about 5 mg to 40 mg per day. An exemplary dosage is about 10 to 30 mg per day. In some embodiments, for a 70 kg human, a suitable dose would be about 0.05 to about 7 g/day, such as about 0.05 to about 2.5 g/day. Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. In some instances, dosage levels below the lower limit of the aforesaid range can be more than adequate, while in other cases still larger doses can be employed without causing any harmful side effect, *e.g.,* by dividing such larger doses into several small doses for administration throughout the day.

[0245] In some embodiments, the compounds can be administered daily, every other day, three times a week, twice a week, weekly, or bi-weekly. The dosing schedule can include a "drug holiday," *e.g.*, the drug can be administered for two weeks on, one week off, or three weeks on, one week off, or four weeks on, one week off, etc., or continuously, without a drug holiday. The compounds can be administered orally, intravenously, intraperitoneally, topically, transdermally, intramuscularly, subcutaneously, intranasally, sublingually, or by any other route.

[0246] In some embodiments, a compound as provided herein is administered in multiple doses. Dosing can be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing can be about once a month, about once every two weeks, about once a week, or about once every other day. In another embodiment, a compound as disclosed herein and another agent are administered together from about once per day to about 6 times per day. In another embodiment, the administration of a compound as provided herein and an agent continues for less than about 7 days. In yet another embodiment, the administration continues for more than about 6 days, about 10 days,

about 14 days, about 28 days, about two months, about six months, or about one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[0247] Administration of the pharmaceutical compositions as disclosed herein can continue as long as necessary. In some embodiments, an agent as disclosed herein is administered for more than about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 14, or about 28 days. In some embodiments, an agent as disclosed herein is administered for less than about 28, about 14, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 day. In some embodiments, an agent as disclosed herein is administered chronically on an ongoing basis, *e.g.,* for the treatment of chronic effects.

[0248] Since the compounds described herein can be administered in combination with other treatments (such as additional chemotherapeutics, radiation or surgery), the doses of each agent or therapy can be lower than the corresponding dose for single-agent therapy. The dose for single-agent therapy can range from, for example, about 0.0001 to about 200 mg, or about 0.001 to about 100 mg, or about 0.01 to about 100 mg, or about 0.1 to about 100 mg, or about 1 to about 50 mg per kilogram of body weight per day. In some embodiments, the dose is about 1 mg/kg, about 5 mg/kg, about 7.5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 50 mg/kg, about 75 mg/kg, or about 100 mg/kg per day. In some embodiments, the dose is about 1 mg/kg, about 7.5 mg/kg, about 20 mg/kg, or about 50 mg/kg per day.

[0249] When a compound provided herein, is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound provided herein unit dose forms of the agent and the compound provided herein can be adjusted accordingly.

3. Kits

[0250] The present disclosure may also relate to kits. The kits can include a compound or pharmaceutical composition as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like. Such kits can 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 pharmaceutical composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information can 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.

[0251] A memory aid may be provided with the kit, *e.g.,* in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.,* as follows "First Week, Monday, Tuesday,... etc.... Second Week, Monday, Tuesday,..."etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day.

[0252] The kit can further contain another agent. The compound as disclosed herein and the agent may be provided as separate pharmaceutical compositions in separate containers within the kit. The compound as disclosed herein and the agent may be provided as a single pharmaceutical 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 can be included in the kit. Kits can further comprise devices that are used to administer the active agents. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits can also be marketed directly to the consumer.

[0253] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. The strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0254] Kits can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active agents. For example, if an active agent is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active agent can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lac-

tated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[0255] The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (*e.g.*, about 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 can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms 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 can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can 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.

Therapeutic Methods

[0256] Phosphoinositide 3-kinases (PI3Ks) are members of a conserved family of lipid kinases that regulate numerous cell functions, including proliferation, differentiation, cell survival and metabolism. Several classes of PI3Ks exist in mammalian cells, including Class IA subgroup (*e.g.*, PI3K-α, β, δ), which are generally activated by receptor tyrosine kinases (RTKs); Class IB (*e.g.,* PI3K-y), which is activated by G-protein coupled receptors (GPCRs), among others. PI3Ks exert their biological activities via a "PI3K-mediated signaling pathway" that includes several components that directly and/or indirectly transduce a signal triggered by a PI3K, including the generation of second messenger phosphotidylinositol, 3,4,5-triphosphate (PIP3) at the plasma membrane, activation of heterotrimeric G protein signaling, and generation of further second messengers such as cAMP, DAG, and IP3, all of which leads to an extensive cascade of protein kinase activation (reviewed in Vanhaesebroeck, B. et al. (2001) Annu Rev Biochem. 70:535-602). For example, PI3K-δ is activated by cellular receptors through interaction between the PI3K regulatory subunit (p85) SH2 domains, or through direct interaction with RAS. PIP3 produced by PI3K activates effector pathways downstream through interaction with plextrin homology (PH) domain containing enzymes (*e.g.*, PDK-1 and AKT [PKB]). (Fung-Leung WP. (2011) Cell Signal. 23(4):603-8). Unlike PI3K-δ, PI3K-γ is not associated with a regulatory subunit of the p85 family, but rather with a regulatory subunit in the p101 family. PI3K-γ is associated with GPCRs, and is responsible for the very rapid induction of PIP3. PI3K-γ can be also activated by RAS.

[0257] The present disclosure generally relates to methods of modulating a PI3 kinase activity (*e.g.*, selectively modulating) by contacting the kinase with an effective amount of a compound as provided herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein. Modulation can be inhibition (*e.g.*, reduction) or activation (*e.g.*, enhancement) of kinase activity. Disclosed herein are methods of inhibiting kinase activity by contacting the kinase with an effective amount of a compound as provided herein in solution. Disclosed herein are methods of inhibiting the kinase activity by contacting a cell, tissue, organ that express the kinase of interest, with a compound provided herein. Also disclosed herein are methods of inhibiting kinase activity in a subject by administering into the subject an effective amount of a compound as provided herein, or a pharmaceutically acceptable form thereof. The kinase activity may be inhibited (*e.g.*, reduced) by more than about 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%, when contacted with a compound provided herein as compared to the kinase activity without such contact. The present disclosure also generally relates to methods of inhibiting PI3 kinase activity in a subject (including mammals such as humans) by contacting said subject with an amount of a compound as provided herein sufficient to inhibit or reduce the activity of the PI3 kinase in said subject.

[0258] The kinase may be a lipid kinase or a protein kinase. The kinase may be selected from a PI3 kinase including different isoforms, such as PI3 kinase α, PI3 kinase β, PI3 kinase γ, PI3 kinase δ; DNA-PK; mTOR; Abl, VEGFR, Ephrin receptor B4 (EphB4); TEK receptor tyrosine kinase (TIE2); FMS-related tyrosine kinase 3 (FLT-3); Platelet derived growth factor receptor (PDGFR); RET; ATM; ATR; hSmg-1; Hck; Src; Epidermal growth factor receptor (EGFR); KIT; Inulsin Receptor (IR); and IGFR.

[0259] As used herein, a "PI3K-mediated disorder" refers to a disease or condition involving aberrant PI3K-mediated signaling pathway. The present disclosure generally relates to a method of treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable form thereof, or a pharmaceutical composition as provided herein. Disclosed herein is a method of treating a PI3K-δ or PI3K-γ mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable form thereof, or a pharmaceutical composition as provided herein. Also disclosed herein is a method for inhibiting at least one of PI3K-δ and PI3K-γ, the

method comprising contacting a cell expressing PI3K *in vitro* or *in vivo* with an effective amount of a compound or composition provided herein. PI3Ks have been associated with a wide range of conditions, including immunity, cancer and thrombosis (reviewed in Vanhaesebroeck, B. et al. (2010) Current Topics in Microbiology and Immunology, DOI 10.1007/82_2010_65). For example, Class I PI3Ks, particularly PI3K-γ and PI3K-δ isoforms, are highly expressed in leukocytes and have been associated with adaptive and innate immunity; thus, these PI3Ks are believed to be important mediators in inflammatory disorders and hematologic malignancies (reviewed in Harris, SJ et al. (2009) Curr Opin Investig Drugs 10(11):1151-62); Rommel C. et al. (2007) Nat Rev Immunol 7(3):191-201; Durand CA et al. (2009) J Immunol. 183(9):5673-84; Dil N, Marshall AJ. (2009) Mol Immunol. 46(10):1970-8; Al-Alwan MM et al. (2007) J Immunol. 178(4):2328-35; Zhang TT, et al. (2008) J Allergy Clin Immunol. 2008;122(4):811-819.e2; Srinivasan L, et al. (2009) Cell 139(3):573-86).

[0260] PI3K-γ is a Class 1B PI3K that associates with the p101 and p84 (p87PIKAP) adaptor proteins, and canonically signals through GPCRs. Non-cononical activation through tyrosine kinase receptors and RAS can occur. Activated PI3K-γ leads to production of PIP3, which serves as a docking site for downstream effector proteins including AKT and BTK, bringing these enzymes to the cell membrane where they may be activated. A scaffolding role for PI3k-y has been proposed and may contribute to the activation of the RAS/MEK/ERK pathway. The interaction with the RAS pathway explains activities attributed to kinase dead PI3K-γ in cells or in animals. PI3K-γ is essential for function of a variety of immune cells and pathways. Chemokine responses (including IL-8, fMLP, and C5a), leading to neutrophil or monocyte cell migration, is dependent on PI3K-γ (HIRSCH et al., "Central Role for G Protein-Coupled Phosphoinositide 3-Kinase γ in Inflammation," Science 287:1049-1053 (2000); SASAKI et al., "Function of PI3Kγ in Thymocyte Development, T Cell Activation, and Neutrophil Migration," Science 287:1040-1046 (2000); LI et al., "Roles of PLC-β2 and -β3 and PI3Kγ in Chemoattractant-Mediated Signal Transduction," Science 287:1046-1049 (2000)). The requirement for PI3K-γ-dependent neutrophil migration is demonstrated by failure of arthritis development in the K/BXN serum transfer arthritis model in PI3K-γ knockout mice (Randis et al., Eur. J. Immunol., 2008, 38(5), 1215-24). Similarly, the mice fail to develop cellular inflammation and airway hyper-responsiveness in the ovalbumin induced asthma model (Takeda et al., J Allergy Clin. Immunol., 2009; 123, 805-12). PI3K-γ deficient mice also have defects in T- helper cell function. T-cell cytokine production and proliferation in response to activation is reduced, and T helper dependent viral clearance is defective (Sasaki et αl., Science, 2000, 287, 1040-46). T cell dependent inflammatory disease models including EAE also do not develop in PI3K-γ deficient mice, and both the T-cell activation defect and cellular migration defects may contribute to efficacy in this model (Comerfold, PLOS One, 2012, 7, e45095). The imiquimod psoriasis model has also been used to demonstrate the importance of PI3K- γ in the inflammatory response. Using PI3K-γ deficient mice in this model, the accumulation of γδ T cells in the skin is blocked, as well as dendritic cell maturation and migration (ROLLER et al., "Blockade of Phosphatidylinositol 3-Kinase (PI3K)δ or PI3Kγ Reduces IL-17 and Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis," J. Immunol. 189:4612-4620 (2012)). The role of PI3K-γ in cellular trafficking can also be demonstrated in oncology models where tumor inflammation is important for growth and metastasis of cancers. In the Lewis Lung Carcinoma model, monocyte activation, migration, and differentiation in tumors are defective. This defect results in a reduction in tumor growth and extended survival in PI3K-γ deficient mice (Schmid et al., Cancer Cell, 2011, 19, 715-27) or upon treatment with inhibitors that target PI3K-γ. In pancreatic cancer, PI3K-γ can be inappropriately expressed, and in this solid tumor cancer or others where PI3K-γ plays a functional role, inhibition of PI3K-γ can be beneficial. Inhibition of PI3K-γ shows promise for the treatment of hematologic malignancies. In a T-ALL model employing a T cell directed knockout of P-Ten, PI3K-δ and PI3K-γ are both essential for the appropriate development of disease, as shown with genetic deletion of both genes (Subramaniam et al. Cancer Cell 21, 459-472, 2012). In addition, in this TALL model, treatment with a small molecule inhibitor of both kinases leads to extended survival of these mice. In CLL, chemokine networks support a pseudo-follicular microenvironment that includes Nurse like cells, stromal cells and T-helper cells. The roles of PI3K-γ in the normal chemokine signaling and T cell biology suggest the value of inhibiting this target in CLL (BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," Curr. Mematol. Malig. Rep. 7:26-33 (2012)). Accordingly, PI3K-γ inhibitors are therapeutically interesting for diseases of the immune system where cell trafficking and T cell or myeloid cell function is important. In oncology, solid tumors that are dependent on tumor inflammation, or tumors with high levels of PI3K-γ expression, may be targeted. For hematological cancers a special role for PI3K-γ and PI3K-δ isoforms in TALL and potentially in CLL suggests targeting these PI3Ks in these diseases.

[0261] Without being limited by a particular theory, PI3K-γ has been shown to play roles in inflammation, arthritis, asthma, allergy, multiple sclerosis (MS), and cancer, among others (*e.g.,* Ruckle et al., Nature Rev., Drug Discovery, 2006, 5, 903-18; Schmid et al., "Myeloid cells in tumor inflammation," Vascular Cell, 2012, doi:10.1186/2045-824X-4-14). For example, PI3K-γ functions in multiple signaling pathways involved in leukocyte activation and migration. PI3K-γ has been shown to drive priming and survival of autoreactive $CD4^+$ T cells during experimental autoimmune encephalomyelitis (EAE), a model for MS. When administered from onset of EAE, a PI3K-γ inhibitor has been shown to cause inhibition and reversal of clinical disease, and reduction of demyelination and cellular pathology in the CNS (Comerford et al., PLOS One, 2012, 7, e45095). PI3K-γ also regulates thymocyte development, T cell activation, neutrophil migration, and

the oxidative burst (Sasaki et al., Science, 2000, 287, 1040-46). In addition, it is shown that allergic airway hyper-responsiveness, inflammation, and remodeling do not develop in PI3K-γ deficient mice (Takeda et al., J. Allergy Clin. Immunol., 2009; 123, 805-12). PI3K-γ is shown to be required for chemoattractant-induced production of phosphatidylinositol 3,4,5-trisphosphate and has an important role in chemoattractant-induced superoxide production and chemotaxis in mouse neutrophils and in production of T cell-independent antigen-specific antibodies composed of the immunoglobulin λ light chain (Li et al., Science, 2000, 287, 1046-49). PI3K-γ is reported to be a crucial signaling molecule required for macrophage accumulation in inflammation (Hirsch et al., Science, 2000, 287, 1049-53). In cancers, pharmacological or genetic blockade of p110γ suppresses inflammation, growth, and metastasis of implanted and spontaneous tumors, suggesting that PI3K-γ can be an important therapeutic target in oncology (Schmid et al., Cancer Cell, 2011, 19, 715-27). For example, it is shown that PI3K-γ has a tumor-specific high accumulation in pancreatic ductal adenocarcinoma (PDAC) in human, signifying a role of PI3K-y in pancreatic cancer (Edling et al., Human Cancer Biology, 2010, 16(2), 4928-37).

[0262] PI3K-δ has roles in impairments of B-cell signaling and development, antibody production, T-cell function, Th1 and Th2 differentiation, and mast and basophil degranulation. Without being limited by a particular theory, PI3K-γ has roles in T-cell function, neutrophil and macrophage recruitment, macrophage activation, neutrophil oxidative burst, and dendritic cell migration. Inhibition of PI3K-δ and/or PI3K-γ isoforms can result in efficacy against inflammation and cancer, *e.g.,* in arthritis, asthma, multiple sclerosis (MS), and tumor models. For example, deficiency in PI3K-δ and/or PI3K-γ can result in efficacy in K/BxN arthritis model (Kyburz et αl., Springer Semin. Immunopathology, 2003, 25, 79-90) or K/BxN serum transfer model of arthritis (Randis et αl., Eur. J. Immunol., 2008, 38(5), 1215-24), where it is shown that recognition of the immune complexes depends on both PI3K-δ and PI3K-γ, whereas cell migration is dependent on PI3K-γ. Deficiency in PI3K-δ or PI3K-γ can also result in efficacy in murine ovalbumin (OVA) induced allergic asthma model (Lee et al., FASEB J., 2006, 20, 455-65; Takeda et al., J. Allergy Clin. Immunol., 2009; 123, 805-12), where it is shown that inhibition of either PI3K-δ or PI3K-γ inhibits ovalbumin induced lung infiltration and improves airway responsiveness. Deficiency in PI3K-δ or PI3K-γ can also result in efficacy in murine experimental autoimmune encephalomyelitis (model for MS), where it is shown that PI3K-γ deletion may provide better efficacy as compared to PI3K-δ deletion (Haylock-Jacob et al., J. Autoimmunity, 2011, 36, 278-87; Comerford et al., PLOS One, 2012, 7, e45095), including reduction in T-cell receptor induced $CD4^+$ T cell activation, leukocyte infiltration and Th1/Th17 responses, and dendritic cell migration (Comerfold, PLOS One, 2012, 7, e45095). Furthermore, inhibition of PI3K-γ can also result in decreased tumor inflammation and growth (*e.g.*, Lewis lung carcinoma model, Schmid et al., Cancer Cell, 2011, 19(6), 715-27). PI3K-γ deletion combined with PI3K-δ deletion results in increased survival in T-cell acute lymphoblastic leukemia (T-ALL) (Subramaniam et al., Cancer Cell, 2012, 21, 459-72). Inhibitors of both PI3K-δ and PI3K-γ are also shown to be efficacious in PTEN-deleted T-ALL cell line (MOLT-4). In the absence of PTEN phosphatase tumor suppressor function, PI3K-δ or PI3K-γ alone can support the development of leukemia, whereas inactivation of both isoforms suppresses tumor formation. Thus, inhibitors of PI3K-δ and/or PI3K-γ can be useful in treating inflammation, such as arthritis, allergic asthma, and MS; and in treating cancer, for example, due to effects such as reductions in solid tumor associated inflammation, angiogenesis and tumor progression.

[0263] The importance of PI3K-δ in the development and function of B-cells is supported from inhibitor studies and genetic models. PI3K-δ is an important mediator of B-cell receptor (BCR) signaling, and is upstream of AKT, calcium flux, PLCγ, MAP kinase, P70S6k, and FOXO3a activation. PI3K-δ is also important in IL4R, SIP, and CXCR5 signaling, and has been shown to modulate responses to toll-like receptors 4 and 9. Inhibitors of PI3K-δ have shown the importance of PI3K-δ in B-cell development (Marginal zone and B1 cells), B-cell activation, chemotaxis, migration and homing to lymphoid tissue, and in the control of immunoglobulin class switching leading to the production of IgE. Clayton E et al. (2002) J Exp Med. 196(6):753-63; Bilancio A, et al. (2006) Blood 107(2):642-50; Okkenhaug K. et al. (2002) Science 297(5583):1031-4; Al-Alwan MM et al. (2007) J Immunol. 178(4):2328-35; Zhang TT, et al. (2008) J Allergy Clin Immunol. 2008;122(4):811-819.e2; SrinivasanL, et al. (2009) Cell 139(3):573-86).

[0264] In T-cells, PI3K-δ has been demonstrated to have a role in T-cell receptor and cytokine signaling, and is upstream of AKT, PLCγ, and GSK3b. In PI3K-δ deletion or kinase-dead knock-in mice, or in inhibitor studies, T-cell defects including proliferation, activation, and differentiation have been observed, leading to reduced T helper cell 2 (TH2) response, memory T-cell specific defects (DTH reduction), defects in antigen dependent cellular trafficking, and defects in chemotaxis/migration to chemokines (*e.g.,* SIP, CCR7, CD62L). (Garçon F. et al. (2008) Blood 111(3):1464-71; Okkenhaug K et al. (2006). J Immunol. 177(8):5122-8; Soond DR, et al. (2010) Blood 115(11):2203-13; Reif K, (2004). J Immunol. 2004;173(4):2236-40; Ji H. et al. (2007) Blood 110(8):2940-7; Webb LM, et al. (2005) J Immunol. 175(5):2783-7; Liu D, et al. (2010) J Immunol. 184(6):3098-105; Haylock-Jacobs S, et al. (2011) J Autoimmun. 2011;36(3-4):278-87; Jarmin SJ, et al. (2008) J Clin Invest. 118(3):1154-64).

[0265] Numerous publications support roles of PI3K-δ and PI3K-γ in the differentiation, maintenance, and activation of immune and malignant cells, as described in more detail herein.

[0266] P13K-δ and PI3K-γ isoforms are preferentially expressed in leukocytes where they have distinct and nonoverlapping roles in immune cell development and function. *See, e.g.,* PURI and GOLD, "Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory disease and

B-cell malignancies," Front. Immunol. 3:256 (2012); BUITENHUIS et al., "The role of the PI3k-PKB signaling module in regulation of hematopoiesis," Cell Cycle 8(4):560-566 (2009); HOELLENRIEGEL and BURGER, "Phosphoinositide 3'-kinase delta: turning off BCR signaling in Chronic Lymphocytic Leukemia," Oncotarget 2(10):737-738 (2011); HIRSCH et al., "Central Role for G Protein-Coupled Phosphoinositide 3-Kinase y in Inflammation," Science 287:1049-1053 (2000); LI et al., "Roles of PLC-β2 and -β3 and PI3Kγ in Chemoattractant-Mediated Signal Transduction," Science 287:1046-1049 (2000); SASAKI et al., "Function of PI3Kγ in Thymocyte Development, T Cell Activation, and Neutrophil Migration," Science 287:1040-1046 (2000); CUSHING et al., "PI3Kδ and PI3Kγ as Targets for Autoimmune and Inflammatory Diseases," J. Med. Chem. 55:8559-8581 (2012); MAXWELL et al., "Attenuation of phosphoinositide 3-kinase δ signaling restrains autoimmune disease," J. Autoimmun. 38:381-391 (2012); HAYLOCK-JACOBS et al., "PI3Kδ drives the pathogenesis of experimental autoimmune encephalomyelitis by inhibiting effector T cell apoptosis and promoting Th17 differentiation," J. Autoimmun. 36:278-287 (2011); SOOND et al., "PI3K p110δ regulates T-cell cytokine production during primary and secondary immune responses in mice and humans," Blood 115(11):2203-2213 (2010); ROLLER et al., "Blockade of Phosphatidylinositol 3-Kinase (PI3K)δ or PI3Kγ Reduces IL-17 and Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis," J. Immunol. 189:4612-4620 (2012); CAMPS et al., "Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis," Nat. Med. 11(9):936-943 (2005). As key enzymes in leukocyte signaling, PI3K-δ and PI3K-γ facilitate normal B-cell, T-cell and myeloid cell functions including differentiation, activation, and migration. *See, e.g.,* HOELLENRIEGEL and BURGER, "Phosphoinositide 3'-kinase delta: turning off BCR signaling in Chronic Lymphocytic Leukemia," Oncotarget 2(10):737-738 (2011); CUSHING et al., "PI3Kδ and PI3Kγ as Targets for Autoimmune and Inflammatory Diseases," J. Med. Chem. 55:8559-8581 (2012). PI3K-δ or PI3K-γ activity is critical for preclinical models of autoimmune and inflammatory diseases. *See, e.g.,* HIRSCH et al., "Central Role for G Protein-Coupled Phosphoinositide 3-Kinase γ in Inflammation," Science 287:1049-1053 (2000); LI et al., "Roles of PLC-β2 and -β3 and PI3Kγ in Chemoattractant-Mediated Signal Transduction," Science 287:1046-1049 (2000); SASAKI et al., "Function of PI3Kγ in Thymocyte Development, T Cell Activation, and Neutrophil Migration," Science 287:1040-1046 (2000); CUSHING et al., "PI3Kδ and PI3Kγ as Targets for Autoimmune and Inflammatory Diseases," J. Med. Chem. 55:8559-8581 (2012); MAXWELL et al., "Attenuation of phosphoinositide 3-kinase δ signaling restrains autoimmune disease," J. Autoimmun. 38:381-391 (2012); HAYLOCK-JACOBS et al., "PI3Kδ drives the pathogenesis of experimental autoimmune encephalomyelitis by inhibiting effector T cell apoptosis and promoting Th17 differentiation," J. Autoimmun. 36:278-287 (2011); SOOND et al., "PI3K p110δ regulates T-cell cytokine production during primary and secondary immune responses in mice and humans," Blood 115(11):2203-2213 (2010); ROLLER et al., "Blockade of Phosphatidylinositol 3-Kinase (PI3K)δ or PI3Kγ Reduces IL-17 and Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis," J. Immunol. 189:4612-4620 (2012); CAMPS et al., "Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis," Nat. Med. 11(9):936-943 (2005). Given the key role for PI3K-δ and PI3K-γ in immune function, inhibitors of the PI3K-δ and/or γ have therapeutic potential in immune-related inflammatory or neoplastic diseases.

[0267] P13K-δ and PI3K-γ are central to the growth and survival of B- and T-cell malignancies and inhibition of these isoforms may effectively limit these diseases. *See, e.g.,* SUBRAMANIAM et al., "Targeting Nonclassical Oncogenes for Therapy in T-ALL," Cancer Cell 21:459-472 (2012); LANNUTTI et al., "CAL-101 a p110δ selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability," Blood 117(2):591-594 (2011). PI3K-δ and PI3K-γ support the growth and survival of certain B-cell malignancies by mediating intracellular BCR signaling and interactions between the tumor cells and their microenvironment. *See, e.g.,* PURI and GOLD, "Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory disease and B-cell malignancies," Front. Immunol. 3:256 (2012); HOELLENRIEGEL et al., "The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leuckemia," Blood 118(13):3603-3612 (2011); BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," Curr. Mematol. Malig. Rep. 7:26-33 (2012). Increased BCR signaling is a central pathologic mechanism of B-cell malignancies and PI3K activation is a direct consequence of BCR pathway activation. *See, e.g.,* BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," Curr. Mematol. Malig. Rep. 7:26-33 (2012); HERISHANU et al., "The lymph node microenvironment promotes B-cell receptor signaling, NF-κB activation, and tumor proliferation in chronic lymphocytic leukemia," Blood 117(2):563-574 (2011); DAVIS et al., "Chronic active B-cell-receptor signaling in diffuse large B-cell lymphoma," Nature 463:88-92 (2010); PIGHI et al., "Phospho-proteomic analysis of mantle cell lymphoma cells suggests a pro-survival role of B-cell receptor signaling," Cell Oncol. (Dordr) 34(2):141-153 (2011); RIZZATTI et al., "Gene expression profiling of mantle cell lymphoma cells reveals aberrant expression of genes from the PI3K-AKT, WNT and TGFβ signaling pathways," Brit. J. Haematol. 130:516-526 (2005); MARTINEZ et al., "The Molecular Signature of Mantle Cell Lymphoma Reveals Multiple Signals Favoring Cell Survival," Cancer Res. 63:8226-8232 (2003). Interactions between malignant B-cells and supporting cells (eg, stromal cells, nurse-like cells) in the tumor microenvironment are important for tumor cell survival, proliferation, homing, and tissue retention. *See, e.g.,* BURGER, "Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia," Curr. Mematol. Malig. Rep. 7:26-33 (2012); HERISHANU et al., "The lymph node microenvironment promotes

B-cell receptor signaling, NF-κB activation, and tumor proliferation in chronic lymphocytic leukemia," Blood 117(2):563-574 (2011); KURTOVA et al., "Diverse marrow stromal cells protect CLL cells from spontaneous and drig-induced apoptosis: development of a reliable and reproducible system to assess stromal cell adhesion-mediated drug resistance," Blood 114(20): 4441-4450 (2009); BURGER et al., "High-level expression of the T-cell chemokines CCL3 and CCL4 by chronic lymphocytic leukemia B cells in nurselike cell cocultures and after BCR stimulation," Blood 113(13) 3050-3058 (2009); QUIROGA et al., "B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406," Blood 114(5):1029-1037 (2009). Inhibiting PI3K-δ,γ with an inhibitor in certain malignant B-cells can block the BCR-mediated intracellular survival signaling as well as key interactions with their microenvironment that are critical for their growth.

[0268] PI3K-δ and PI3K-γ also play a direct role in the survival and proliferation of certain T-cell malignancies. *See, e.g.,* SUBRAMANTAM et al., "Targeting Nonclassical Oncogenes for Therapy in T-ALL," Cancer Cell 21:459-472 (2012). Aberrant PI3K-δ and PI3K-γ activity provides the signals necessary for the development and growth of certain T-cell malignancies. While BTK is expressed in B-cells, it is not expressed in T-cells, and therefore BTK is not a viable target for the treatment of T-cell malignancies. *See, e.g.,* NISITANI et al., "Posttranscriptional regulation of Bruton's tyrosine kinase expression in antigen receptor-stimulated splenic B cells," PNAS 97(6):2737-2742 (2000); DE WEERS et al., "The Bruton's tyrosine kinase gene is expressed throughout B cell differentiation, from early precursor B cell stages preceding immunoglobulin gene rearrangement up to mature B cell stages," Eur. J. Immunol. 23:3109-3114 (1993); SMITH et al., "Expression of Bruton's Agammaglobulinemia Tyrosine Kinase Gene, BTK, Is Selectively Down-Regulated in T Lymphocytes and Plasma Cells," J. Immunol. 152:557-565 (1994). PI3K-δ and/or y inhibitors may have unique therapeutic potential in T-cell malignancies.

[0269] In neutrophils, PI3K-δ, along with PI3K-γ, contribute to the responses to immune complexes, FCγRII signaling, including migration and neutrophil respiratory burst. Human neutrophils undergo rapid induction of PIP3 in response to formyl peptide receptor (FMLP) or complement component C5a (C5a) in a PI3K-γ dependent manner, followed by a longer PIP3 production period that is PI3K-δ dependent, and is essential for respiratory burst. The response to immune complexes is contributed by PI3K-δ, PI3K-γ, and PI3K-β, and is an important mediator of tissue damage in models of autoimmune disease (Randis TM et al. (2008) Eur J Immunol. 38(5):1215-24; Pinho V, (2007) J Immunol. 179(11):7891-8; Sadhu C. et al. (2003) J Immunol. 170(5):2647-54 ; Condliffe AM et al. (2005) Blood 106(4):1432-40). It has been reported that in certain autoimmune diseases, preferential activation of PI3K-β may be involved (Kulkarni et al., Immunology (2011) 4(168) ra23: 1-11). It was also reported that PI3K-β-deficient mice were highly protected in an FcyR-dependent model of autoantibody-induced skin blistering and partially protected in an FcyR-dependent model of inflammatory arthritis, whereas combined deficiency of PI3K-β and PI3K-δ resulted in near complete protection in inflammatory arthritis (*Id.*).

[0270] In macrophages collected from patients with chronic obstructive pulmonary disease (COPD), glucocorticoid responsiveness can be restored by treatment of the cells with inhibitors of PI3K-δ. Macrophages also rely on PI3K-δ and PI3K-γ for responses to immune complexes through the arthus reaction (FCγR and C5a signaling) (Randis TM, et al. (2008) Eur J Immunol. 38(5):1215-24 ; Marwick JA et al. (2009) Am J Respir Crit Care Med. 179(7):542-8; Konrad S, et al. (2008) J Biol Chem. 283(48):33296-303).

[0271] In mast cells, stem cell factor- (SCF) and IL3-dependent proliferation, differentiation and function are PI3K-δ dependent, as is chemotaxis. The allergen/IgE crosslinking of FCγR1 resulting in cytokine release and degranulation of the mast cells is severely inhibited by treatment with PI3K-δ inhibitors, suggesting a role for PI3K-δ in allergic disease (Ali K et al. (2004) Nature 431(7011):1007-11; Lee KS, et al. (2006) FASEB J. 20(3):455-65; Kim MS, et al. (2008) Trends Immunol. 29(10):493-501).

[0272] Natural killer (NK) cells are dependent on both PI3K-δ and PI3K-γ for efficient migration towards chemokines including CXCL10, CCL3, SIP and CXCL12, or in response to LPS in the peritoneum (Guo H, et al. (2008) J Exp Med. 205(10):2419-35; Tassi I, et al. (2007) Immunity 27(2):214-27; Saudemont A, (2009) Proc Natl Acad Sci US A. 106(14):5795-800; Kim N, et al. (2007) Blood 110(9):3202-8).

[0273] The roles of PI3K-δ and PI3K-γ in the differentiation, maintenance, and activation of immune cells support a role for these enzymes in inflammatory disorders ranging from autoimmune diseases (*e.g.*, rheumatoid arthritis, multiple sclerosis) to allergic inflammatory disorders, such as asthma, and inflammatory respiratory disease, such as COPD. Extensive evidence is available in experimental animal models, or can be evaluated using art-recognized animal models.

[0274] For example, inhibitors of PI3K-δ and/or -γ have been shown to have anti-inflammatory activity in several autoimmune animal models for rheumatoid arthritis (Williams, O. et al. (2010) Chem Biol, 17(2):123-34; WO 2009/088986; WO2009/088880; WO 2011/008302). PI3K-δ is expressed in the RA synovial tissue (especially in the synovial lining which contains fibroblast-like synoviocytes (FLS), and selective PI3K-δ inhibitors have been shown to be effective in inhibiting synoviocyte growth and survival (Bartok et al. (2010) Arthritis Rheum 62 Suppl 10:362). Several PI3K-δ and -γ inhibitors have been shown to ameliorate arthritic symptoms (*e.g.,* swelling of joints, reduction of serum-induced collagen levels, reduction of joint pathology and/or inflammation), in art-recognized models for RA, such as collagen-induced arthritis and adjuvant induced arthritis (WO 2009/088986; WO2009/088880; WO 2011/008302;).

[0275] The role of PI3K-δ has also been shown in models of T-cell dependent response, including the DTH model. In the murine experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis, the PI3K-γ/δ- double mutant mice are resistant. PI3K-δ inhibitors have also been shown to block EAE disease induction and development of TH-17 cells both *in vitro* and *in vivo* (Haylock-Jacobs, S. et al. (2011) J. Autoimmunity 36(3-4):278-87).

[0276] Systemic lupus erythematosus (SLE) is a complex disease that at different stages requires memory T-cells, B-cell polyclonal expansion and differentiation into plasma cells, and the innate immune response to endogenous damage associated molecular pattern molecules (DAMPS), and the inflammatory responses to immune complexes through the complement system as well as the F_C receptors. The role of PI3K-δ and PI3K-γ together in these pathways and cell types suggest that blockade with an inhibitor would be effective in these diseases. A role for PI3K in lupus is also predicted by two genetic models of lupus. The deletion of phosphatase and tensin homolog (PTEN) leads to a lupus-like phenotype, as does a transgenic activation of Class 1A PI3Ks, which includes PI3K-δ. The deletion of PI3K-γ in the transgenically activated class 1A lupus model is protective, and treatment with a PI3K-γ selective inhibitor in the murine *MLR/lpr* model of lupus improves symptoms (Barber, DF et al. (2006) J. Immunol. 176(1): 589-93).

[0277] In allergic disease, PI3K-δ has been shown by genetic models and by inhibitor treatment to be essential for mast-cell activation in a passive cutaneous anaphalaxis assay (Ali K et al. (2008) J Immunol. 180(4):2538-44; Ali K, (2004) Nature 431(7011):1007-11). In a pulmonary measure of response to immune complexes (Arthus reaction) a PI3K-δ knockout is resistant, showing a defect in macrophage activation and C5a production. Knockout studies and studies with inhibitors for both PI3K-δ and PI3K-γ support a role for both of these enzymes in the ovalbumin induced allergic airway inflammation and hyper-responsiveness model (Lee KS et al. (2006) FASEB J. 20(3):455-65). Reductions of infiltration of eosinophils, neutrophils, and lymphocytes as well as TH2 cytokines (IL4, IL5, and IL13) were seen with both PI3K-δ specific and dual PI3K-δ and PI3K-γ inhibitors in the Ova induced asthma model (Lee KS et al. (2006) J Allergy Clin Immunol 118(2):403-9).

[0278] P13K-δ and PI3K-γ inhibition can be used in treating COPD. In the smoked mouse model of COPD, the PI3K-δ knockout does not develop smoke induced glucocorticoid resistance, while wild-type and PI3K-γ knockout mice do. An inhaled formulation of dual PI3K-δ and PI3K-γ inhibitor blocked inflammation in a LPS or smoke COPD models as measured by neutrophilia and glucocorticoid resistance (Doukas J, et al. (2009) J Pharmacol Exp Ther. 328(3):758-65).

[0279] Class I PI3Ks, particularly PI3K-δ and PI3K-γ isoforms, are also associated with cancers (reviewed, *e.g.*, in Vogt, PK et al. (2010) Curr Top Microbiol Immunol. 347:79-104; Fresno Vara, JA et al. (2004) Cancer Treat Rev. 30(2):193-204; Zhao, L and Vogt, PK. (2008) Oncogene 27(41):5486-96). Inhibitors of PI3K, *e.g.,* PI3K-δ and/or PI3K-γ, have been shown to have anti-cancer activity (*e.g.,* Courtney, KD et al. (2010) J Clin Oncol. 28(6):1075-1083); Markman, B et al. (2010) Ann Oncol. 21(4):683-91; Kong, D and Yamori, T (2009) Curr Med Chem. 16(22):2839-54; Jimeno, A et al. (2009) J Clin Oncol. 27:156s (suppl; abstr 3542); Flinn, IW et al. (2009) J Clin Oncol. 27:156s (suppl; abstr 3543); Shapiro, Get al. (2009) J Clin Oncol. 27:146s (suppl; abstr 3500); Wagner, AJ et al. (2009) J Clin Oncol. 27:146s (suppl; abstr 3501); Vogt, PK et al. (2006) Virology 344(1):131-8; Ward, S et al. (2003) Chem Biol. 10(3):207-13; WO 2011/041399; US 2010/0029693; US 2010/0305096; US 2010/0305084).

[0280] The present disclosure relates to a method of treating cancer. Types of cancer that can be treated with an inhibitor of PI3K (particularly, PI3K-δ and/or PI3K-y) include, e.g., leukemia, chronic lymphocytic leukemia, acute myeloid leukemia *(e.g.,* Salmena, L et al. (2008) Cell 133:403-414; Chapuis, N et al. (2010) Clin Cancer Res. 16(22):5424-35; Khwaja, A (2010) Curr Top Microbiol Immunol. 347:169-88); lymphoma, *e.g.,* non-Hodgkin's lymphoma *(e.g.,* Salmena, L et al. (2008) Cell 133:403-414); lung cancer, *e.g.,* non-small cell lung cancer (*e.g.,* Herrera, VA et al. (2011) Anticancer Res. 31(3):849-54); melanoma *(e.g.,* Haluska, F et al. (2007) Semin Oncol. 34(6):546-54); prostate cancer (*e.g.,* Sarker, D et al. (2009) Clin Cancer Res. 15(15):4799-805); glioblastoma (*e.g.,* Chen, JS et al. (2008) Mol Cancer Ther. 7:841-850); endometrial cancer (*e.g.,* Bansal, Net al. (2009) Cancer Control. 16(1):8-13); pancreatic cancer *(e.g.,* Furukawa, T (2008) J Gastroenterol. 43(12):905-11); renal cell carcinoma *(e.g.,* Porta, C and Figlin, RA (2009) J Urol. 182(6):2569-77); colorectal cancer (*e.g.,* Saif, MW and Chu, E (2010) Cancer J. 16(3):196-201); breast cancer *(e.g.,* Torbett, NE et al. (2008) Biochem J. 415:97-100); and ovarian cancer *(e.g.,* Mazzoletti, M and Broggini, M (2010) Curr Med Chem. 17(36):4433-47).

[0281] Numerous publications support a role of PI3K-δ and PI3K-γ in treating hematological cancers. PI3K-δ and PI3K-γ are highly expressed in the heme compartment, and some solid tumors, including prostate, breast and glioblastomas (Chen J.S. et al. (2008) Mol Cancer Ther. 7(4):841-50; Ikeda H. et al. (2010) Blood 116(9):1460-8).

[0282] In hematological cancers including acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL), overexpression and constitutive activation of PI3K-δ supports the model that PI3K-δ inhibition would be therapeutic Billottet C, et al. (2006) Oncogene 25(50):6648-59; Billottet C, et al. (2009) Cancer Res. 69(3):1027-36; Meadows, SA, 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Ikeda H, et al. (2010) Blood 116(9):1460-8; Herman SE et al. (2010) Blood 116(12):2078-88; Herman SE et al. (2011). Blood 117(16):4323-7.

[0283] The present disclosure relates to a method of treating hematological cancers including, but not limited to acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL).

[0284] A PI3K-δ inhibitor (CAL-101) has been evaluated in a phase 1 trial in patients with haematological malignancies, and showed activity in CLL in patients with poor prognostic characteristics. In CLL, inhibition of PI3K-δ not only affects tumor cells directly, but it also affects the ability of the tumor cells to interact with their microenvironment. This microenvironment includes contact with and factors from stromal cells, T-cells, nurse like cells, as well as other tumor cells. CAL-101 suppresses the expression of stromal and T-cell derived factors including CCL3, CCL4, and CXCL13, as well as the CLL tumor cells' ability to respond to these factors. CAL-101 treatment in CLL patients induces rapid lymph node reduction and redistribution of lymphocytes into the circulation, and affects tonic survival signals through the BCR, leading to reduced cell viability, and an increase in apoptosis. Single agent CAL-101 treatment was also active in mantle cell lymphoma and refractory non Hodgkin's lymphoma (Furman, RR, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Hoellenriegel, J, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Webb, HK, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Meadows, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Kahl, B, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Lannutti BJ, et al. (2011) Blood 117(2):591-4).

[0285] P13K-δ inhibitors have shown activity against PI3K-δ positive gliomas *in vitro* (Kashishian A, et al. Poster presented at: The American Association of Cancer Research 102nd Annual Meeting; 2011 Apr 2-6; Orlando, FL). PI3K-δ is the PI3K isoform that is most commonly activated in tumors where the PTEN tumor suppressor is mutated (Ward S, et al. (2003) Chem Biol. 10(3):207-13). In this subset of tumors, treatment with the PI3K-δ inhibitor either alone or in combination with a cytotoxic agent can be effective.

[0286] Another mechanism for PI3K-δ inhibitors to have an effect in solid tumors involves the tumor cells' interaction with their micro-environment. PI3K-δ, PI3K-γ, and PI3K-β are expressed in the immune cells that infiltrate tumors, including tumor infiltrating lymphocytes, macrophages, and neutrophils. PI3K-δ inhibitors can modify the function of these tumor-associated immune cells and how they respond to signals from the stroma, the tumor, and each other, and in this way affect tumor cells and metastasis (Hoellenriegel, J, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL).

[0287] P13K-δ is also expressed in endothelial cells. It has been shown that tumors in mice treated with PI3K-δ selective inhibitors are killed more readily by radiation therapy. In this same study, capillary network formation is impaired by the PI3K inhibitor, and it is postulated that this defect contributes to the greater killing with radiation. PI3K-δ inhibitors can affect the way in which tumors interact with their microenvironment, including stromal cells, immune cells, and endothelial cells and be therapeutic either on its own or in conjunction with another therapy (Meadows, SA, et al. Paper presented at: 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; GengL, et al. (2004) Cancer Res. 64(14):4893-9).

[0288] The present disclosure relates to a method of treating or preventing a cancer or disease, such as hematologic malignancy, or a specific type or sub-type of cancer or disease, such as a specific type or sub-type of hematologic malignancy, with a PI3K-γ selective inhibitor, wherein the adverse effects associated with administration of inhibitors for other isoform(s) of PI3K (*e.g.,* PI3K-α and/or PI3K-β) are reduced. Disclosed herein is a method of treating or preventing a cancer or disease, such as hematologic malignancy, or a specific type or sub-type of cancer or disease, such as a specific type or sub-type of hematologic malignancy, with a PI3K-γ selective inhibitor, at a lower (*e.g.*, by about 10%, by about 20%, by about 30%, by about 40%, by about 50%, by about 60%, by about 70%, or by about 80%) dose as compared to treatment with a PI3K-γ non-selective or less selective PI3K-γ inhibitor (*e.g.,* a PI3Kpan inhibitors, e.g., inhibiting PI3K-α, β, δ, and γ).

[0289] The role of PI3K-γ pathway in promoting myeloid cell trafficking to tumors and the role of blockade of p100γ in suppression of tumor inflammation and growth in breast cancer, pancreatic cancer, and lung cancer are reported, for example, in Schmid et al. (2011) Cancer Cell 19, 715-727. The present disclosure relates to a method of treating or preventing pancreatic cancer with a PI3K inhibitor. Also disclosed herein is a method of treating or preventing breast cancer with a PI3K inhibitor. Further disclosed herein is a method of treating or preventing lung cancer with a PI3K inhibitor. The PI3K inhibitor may be a PI3K-γ inhibitor, selective or non-selective over one or more other PI3K isoform(s). The PI3K inhibitor may be a PI3K-γ selective inhibitor.

[0290] Without being limited by a particular theory selectively inhibiting PI3K-γ isoform can provide a treatment regimen where adverse effects associated with administration of a non-selective PI3K inhibitor are minimized or reduced. Without being limited by a particular theory selectively inhibiting PI3K-δ isoform can provide a treatment regimen where adverse effects associated with administration of a non-selective PI3K inhibitor are minimized or reduced. Without being limited by a particular theory selectively inhibiting PI3K-δ and γ isoform can provide a treatment regimen where adverse effects associated with administration of a non-selective PI3K inhibitor are minimized or reduced. Without being limited by a particular theory, it is believed that the adverse effects can be reduced by avoiding the inhibition of other isoforms (e.g., α or β) of PI3K.

[0291] The adverse effect may be hyperglycemia. The adverse effect may be rash. The adverse effect may be impaired male fertility that may result from inhibition of β isoform of PI3K (*see, e.g.,* Ciraolo et al., Molecular Biology of the Cell, 21: 704-711 (2010)). The adverse effect may be testicular toxicity that may result from inhibition of PI3K-β (*see, e.g.,*

Wisler et al., Amgen SOT, Abstract ID # 2334 (2012)). The adverse effect may be embryonic lethality (*see, e.g.,* Bi et al., J Biol Chem, 274: 10963-10968 (1999)). The adverse effect may be defective platelet aggregation (*see, e.g.,* Kulkarni et al., Science, 287: 1049-1053 (2000)). The adverse effect may be functionally defective neutrophil (*id.*).

[0292] The PI3K-γ inhibitor may selectively modulate phosphatidyl inositol-3 kinase (PI3 kinase) gamma isoform. The PI3K-γ inhibitor may selectively inhibit the gamma isoform over the alpha, beta, or delta isoform. The PI3K-γ inhibitor may selectively inhibit the gamma isoform over the alpha or beta isoform. The PI3K-γ inhibitor may selectively inhibit the gamma isoform over the alpha, beta, and delta isoforms. The PI3K-γ inhibitor may selectively inhibit the gamma isoform over the alpha and beta isoforms. The PI3K-γ inhibitor may selectively inhibit the gamma isoform over the alpha and beta isoforms, but not the delta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by ratio of IC_{50} values, among other means. The selectivity of PI3K gamma isoform over an other PI3K isoform may be measured by the ratio of the IC_{50} value against the other PI3K isoform to the IC_{50} value against PI3K gamma isoform. The PI3 kinase gamma isoform IC_{50} activity of a compound as disclosed herein can be less than about 1000 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM. For example, a compound that selectively inhibits one isoform of PI3K over another isoform of PI3K has an activity of at least 2X against a first isoform relative to the compound's activity against the second isoform (*e.g.,* at least about 3X, 5X, 10X, 20X, 50X, 100X, 200X, 500X, or 1000X).

[0293] The present disclosure also relates to a method for treating rheumatoid arthritis or asthma in a subject, or for reducing a rheumatoid arthritis-associated symptom or an asthma-associated symptom in a subject, comprising administering an effective amount of a PI3K-γ inhibitor to a subject in need thereof, wherein one or more of the adverse effects associated with administration of inhibitors for one or more other isoforms of PI3K are reduced. The one or more other isoforms of PI3K may be PI3K-α, PI3K-β, and/or PI3K-δ. The one or more other isoforms of PI3K may be PI3K-α and/or PI3K-β. The method may be for treating rheumatoid arthritis in a subject, or for reducing a rheumatoid arthritis-associated symptom in a subject. The method may be for treating asthma in a subject, or for reducing an asthma-associated symptom in a subject.

[0294] Patients that can be treated with a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, according to the methods as disclosed herein include, for example, but are not limited to, patients that have been diagnosed as having breast cancer; ovarian cancer; uterine cancer; cervical cancer; prostate cancer; pancreatic cancer; bladder cancer such as a transitional cell carcinoma in urinary bladder or urothelial carcinoma; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and myelodysplastic syndrome (MDS); lung cancer such as non-small cell lung cancer (NSCLC); skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma; kidney cancer; lymphoma such as diffuse large B-cell lymphoma; viral-induced cancers; cervical cancer; and testicular cancer.

[0295] Patients that can be treated with compounds provided herein, or pharmaceutically acceptable salt, ester solvate, hydrate or derivative of said compounds, according to the methods disclosed herein include, for example, patients that have been diagnosed as having conditions including, but not limited to, adenocarcinoma, adrenal gland cancer, angiosarcoma (e.g., lymphangiosarcoma, lymphangioendotheliosarcoma), breast cancer, brain cancer, cervical cancer, chordoma, colorectal cancer, endotheliosarcoma, endometrial cancer, gastric cancer, gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma, kidney cancer (e.g., renal cell carcinoma), liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma), lung cancer (e.g., bronchogenic carcinoma, non-small cell lung cancer (NSCLC)), leukemia (e.g., acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL) and Waldenstrom's macroglobulinemia (WM); peripheral T cell lymphomas (PTCL), adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGL); acute myelocytic leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL)), lymphoma (e.g., Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL)), leiomyosarcoma (LMS), mastocytosis, multiple myeloma (MM), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD), neuroendocrine cancer, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer (, skin cancer (e.g., squamous cell carcinoma (SCC), basal cell carcinoma (BCC)), soft tissue sarcoma (e.g., liposarcoma, chondrosarcoma, myxosarcoma), testicular cancer, and Waldenström's macroglobulinemia.

[0296] Without being limited by a particular theory, the cancer or disease being treated or prevented, such as a blood disorder or hematologic malignancy, may have a high expression level of one or more PI3K isoform(s) (e.g., PI3K-α,

PI3K-β, PI3K-δ, or PI3K-γ, or a combination thereof). The cancer or disease that can be treated or prevented by methods, compositions, or kits disclosed herein may include a blood disorder or a hematologic malignancy, including, but not limited to, myeloid disorder, lymphoid disorder, leukemia, lymphoma, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), mast cell disorder, and myeloma (e.g., multiple myeloma), among others. The blood disorder or the hematologic malignancy may include, but is not limited to, acute lymphoblastic leukemia (ALL), T-cell ALL (T-ALL), B-cell ALL (B-ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), blast phase CML, small lymphocytic lymphoma (SLL), CLL/SLL, blast phase CLL, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), B-cell NHL, T-cell NHL, indolent NHL (iNHL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), aggressive B-cell NHL, B-cell lymphoma (BCL), Richter's syndrome (RS), T-cell lymphoma (TCL), peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), transformed mycosis fungoides, Sézary syndrome, anaplastic large-cell lymphoma (ALCL), follicular lymphoma (FL), Waldenstrom macroglobulinemia (WM), lymphoplasmacytic lymphoma, Burkitt lymphoma, multiple myeloma (MM), amyloidosis, MPD, essential thrombocytosis (ET), myelofibrosis (MF), polycythemia vera (PV), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS), angioimmunoblastic lymphoma, high-risk MDS, and low-risk MDS. The hematologic malignancy may be relapsed. The hematologic malignancy may be refractory. The cancer or disease may be in a pediatric patient (including an infantile patient). The cancer or disease may be in an adult patient. The treatment or prevention of a cancer or disease by methods, compositions, or kits disclosed herein are further discussed herein elsewhere.

[0297] The cancer or hematologic malignancy may be CLL. The cancer or hematologic malignancy may be CLL/SLL. The cancer or hematologic malignancy may be blast phase CLL. The cancer or hematologic malignancy may be SLL.

[0298] The cancer or hematologic malignancy may be iNHL. The cancer or hematologic malignancy may be DLBCL. The cancer or hematologic malignancy maybe B-cell NHL (*e.g.,* aggressive B-cell NHL). The cancer or hematologic malignancy may be MCL. The cancer or hematologic malignancy may be RS. The cancer or hematologic malignancy may be AML. The cancer or hematologic malignancy may be MM. The cancer or hematologic malignancy may be ALL. The cancer or hematologic malignancy may be T-ALL. The cancer or hematologic malignancy may be B-ALL. The cancer or hematologic malignancy may be TCL. The cancer or hematologic malignancy may be ALCL. The cancer or hematologic malignancy may be leukemia. The cancer or hematologic malignancy may be lymphoma. The cancer or hematologic malignancy may be T-cell lymphoma. The cancer or hematologic malignancy may be MDS (e.g., low grade MDS). The cancer or hematologic malignancy may be MPD. The cancer or hematologic malignancy may be a mast cell disorder. The cancer or hematologic malignancy may be Hodgkin lymphoma (HL). The cancer or hematologic malignancy may be non-Hodgkin lymphoma. The cancer or hematologic malignancy may be PTCL. The cancer or hematologic malignancy may be CTCL (e.g., mycosis fungoides or Sezary syndrome). The cancer or hematologic malignancy may be WM. The cancer or hematologic malignancy may be CML. The cancer or hematologic malignancy may be FL. The cancer or hematologic malignancy may be transformed mycosis fungoides. The cancer or hematologic malignancy may be Sezary syndrome. The cancer or hematologic malignancy may be acute T-cell leukemia. The cancer or hematologic malignancy may be acute B-cell leukemia. The cancer or hematologic malignancy may be Burkitt lymphoma. The cancer or hematologic malignancy may be myeloproliferative neoplasms. The cancer or hematologic malignancy may be splenic marginal zone. The cancer or hematologic malignancy may be nodal marginal zone. The cancer or hematologic malignancy may be extranodal marginal zone.

[0299] The cancer or hematologic malignancy may be a B cell lymphoma. The present disclosure also relates to a method of treating or managing a B cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. Also disclosed herein is a method of treating or lessening one or more of the symptoms associated with a B cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. The B cell lymphoma may be iNHL. The B cell lymphoma may be follicular lymphoma. The B cell lymphoma may be Waldenstrom macroglobulinemia (lymphoplasmacytic lymphoma). The B cell lymphoma may be marginal zone lymphoma (MZL). The B cell lymphoma may be MCL. The B cell lymphoma may be HL. The B cell lymphoma may be aNHL. The B cell lymphoma may be DLBCL. The B cell lymphoma may be Richters lymphoma.

[0300] The cancer or hematologic malignancy may be a T cell lymphoma. The present disclosure also relates to a method of treating or managing a T cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. Also disclosed herein is a method of treating or lessening one or more of the symptoms associated with a T cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. The T cell lymphoma may be peripheral T cell lymphoma (PTCL). The T cell lymphoma may be cutaneous T cell lymphoma (CTCL).

[0301] The cancer or hematologic malignancy may be Sezary syndrome. The present disclosure also relates to a method of treating or managing Sezary syndrome comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. Also disclosed

herein is a method of treating or lessening one or more of the symptoms associated with Sezary syndrome comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof. The symptoms associated with Sezary syndrome include, but are not limited to, epidermotropism by neoplastic CD4+ lymphocytes, Pautrier's microabscesses, erythroderma, lymphadenopathy, atypical T cells in the peripheral blood, and hepatosplenomegaly. The therapeutically effective amount for treating or managing Sezary syndrome may be from about 25 mg to 75 mg, administered twice daily. The therapeutically effective amount may be from about 50 mg to about 75 mg, from about 30 mg to about 65 mg, from about 45 mg to about 60 mg, from about 30 mg to about 50 mg, or from about 55 mg to about 65 mg, each of which is administered twice daily. The effective amount may be about 60 mg, administered twice daily.

[0302] The cancer or hematologic malignancy may be relapsed. The cancer or hematologic malignancy may be refractory. The cancer being treated or prevented may be a specific sub-type of cancer described herein. The hematologic malignancy being treated or prevented may be a specific sub-type of hematologic malignancy described herein. Certain classifications of type or sub-type of a cancer or hematologic malignancy disclosed herein are known in the art. Without being limited by a particular theory, it is believed that many of the cancers that become relapsed or refractory develop resistance to the particular prior therapy administered to treat the cancers. Thus, without being limited by a particular theory, a compound provided herein can provide a second line therapy by providing an alternative mechanism to treat cancers different from those mechanisms utilized by certain prior therapies. Accordingly, disclosed herein is a method of treating or managing cancer or hematologic malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, wherein the cancer or hematologic malignancy is relapsed after, or refractory to, a prior therapy.

[0303] The cancer or hematologic malignancy may be refractory iNHL. The cancer or hematologic malignancy may be refractory CLL. The cancer or hematologic malignancy may be refractory SLL. The cancer or hematologic malignancy may be refractory to rituximab therapy. The cancer or hematologic malignancy may be refractory to chemotherapy. The cancer or hematologic malignancy may be refractory to radioimmunotherapy (RIT). The cancer or hematologic malignancy may be iNHL, FL, splenic marginal zone, nodal marginal zone, extranodal marginal zone, or SLL.The cancer or hematologic malignancy may be refractory to rituximab therapy, chemotherapy, and/or RIT.

[0304] The cancer or hematologic malignancy may be lymphoma, and the cancer may be relapsed after, or refractory to, the treatment by a BTK inhibitor such as, but not limited to, ibrutinib. The cancer or hematologic malignancy may be CLL, and the cancer may be relapsed after, or refractory to, the treatment by a BTK inhibitor such as, but not limited to, ibrutinib and AVL-292.

[0305] The present disclosure also relates to a method of treating an inflammation disorder, including autoimmune diseases in a subject. The method comprises administering to said subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein. Examples of autoimmune diseases include but are not limited to acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, autoimmune skin disease, coeliac disease, Crohn's disease, Diabetes mellitus (type 1), Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, lupus erythematosus, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, oemphigus, polyarthritis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis (also known as "giant cell arteritis"), warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis (e.g., inflammatory alopecia), Chagas disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, and vulvodynia. Other disorders include bone-resorption disorders and thrombosis.

[0306] Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[0307] Exemplary inflammatory conditions include, but are not limited to, inflammation associated with acne, anemia (*e.g.,* aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (*e.g.,* polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (e.g., crystalline arthritis, osteoarthritis, psoriatic arthritis, gout flare, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, diverticulitis, diabetes (*e.g.,* type I diabetes mellitus, type 2 diabetes mellitus), a skin condition *(e.g.,* psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus

and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (e.g., eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.,* Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, polymyalgia rheumatic, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, scleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis. The inflammatory disorder may be selected from arthritis (*e.g.*, rheumatoid arthritis), inflammatory bowel disease, inflammatory bowel syndrome, asthma, psoriasis, endometriosis, interstitial cystitis and prostatistis. The inflammatory condition may be an acute inflammatory condition (*e.g.*, for example, inflammation resulting from infection). The inflammatory condition may be a chronic inflammatory condition (e.g., conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds can also be useful in treating inflammation associated with trauma and non-inflammatory myalgia.

[0308] Immune disorders, such as auto-immune disorders, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthopathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.,* eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.,* Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), relapsing polychondritis (e.g., atrophic polychondritis and systemic polychondromalacia), and disorders ameliorated by a gastroprokinetic agent (*e.g.,* ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)). The present disclosure relates to a method of treating inflammatory or autoimmune diseases comprising administering to a subject (*e.g., a* mammal) a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, that selectively inhibit PI3K-δ and/or PI3K-γ as compared to all other type I PI3 kinases. Such selective inhibition of PI3K-δ and/or PI3K-γ can be advantageous for treating any of the diseases or conditions described herein. For example, selective inhibition of PI3K-δ and/or PI3K-γ can inhibit inflammatory responses associated with inflammatory diseases, autoimmune disease, or diseases related to an undesirable immune response including, but not limited to asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, psoriasis, lupus erythematosus, anaphylaxsis, or graft versus host disease. Selective inhibition of PI3K-δ and/or PI3K-γ can further provide for a reduction in the inflammatory or undesirable immune response without a concomitant reduction in the ability to reduce a bacterial, viral, and/or fungal infection. Selective inhibition of both PI3K-δ and PI3K-γ can be advantageous for inhibiting the inflammatory response in the subject to a greater degree than that would be provided for by inhibitors that selectively inhibit PI3K -δ or PI3K-γ alone. In one aspect, one or more of the subject methods are effective in reducing antigen specific antibody production *in vivo* by about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more. In another aspect, one or more of the subject methods are effective in reducing antigen specific IgG3 and/or IgGM production *in vivo by* about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more.

[0309] One or more of the methods disclosed herein may be effective in ameliorating symptoms associated with rheumatoid arthritis including, but not limited to a reduction in the swelling of joints, a reduction in serum anti-collagen levels, and/or a reduction in joint pathology such as bone resorption, cartilage damage, pannus, and/or inflammation. The methods disclosed herein may be effective in reducing ankle inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, or 60%, or about 75% to 90%. The methods disclosed herein may be effective in reducing knee inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, or 60%, or about 75% to 90% or more. The methods disclosed herein may be effective in reducing serum anti-type II collagen levels by at least about 10%, 12%, 15%, 20%, 24%, 25%, 30%, 35%, 50%, 60%, 75%, 80%, 86%, or 87%, or about 90% or more. The methods disclosed

herein may be effective in reducing ankle histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, or 90%, or more. The methods disclosed herein may be effective in reducing knee histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, or 90%, or more.

[0310] The present disclosure also relates to methods for treating disorders or conditions in which the δ isoform of PI3K is implicated to a greater extent than other PI3K isoforms such as PI3K-α and/or PI3K-β. Disclosed herein are methods for treating disorders or conditions in which the γ isoform of PI3K is implicated to a greater extent than other PT3K isoforms such as PI3K-α and/or PI3K-β. Selective inhibition of PI3K-δ and/or PI3K-γ can provide advantages over using less selective compounds which inhibit PI3K-α and/or PI3K-β, such as an improved side effects profile or lessened reduction in the ability to reduce a bacterial, viral, and/or fungal infection.

[0311] The present disclosure also relates to methods of using a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, to treat respiratory diseases including, but not limited to, diseases affecting the lobes of lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract, or the nerves and muscle for breathing. For example, methods are disclosed to treat obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is an umbrella term for a group of respiratory tract diseases that are characterized by airflow obstruction or limitation. Conditions included in this umbrella term include, but are not limited to: chronic bronchitis, emphysema, and bronchiectasis.

[0312] A compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein may be used for the treatment of asthma. The compounds or pharmaceutical compositions described herein may be used for the treatment of rheumatoid arthritis (RA).

[0313] Efficacy of a compound provided herein in treating, preventing and/or managing the disease or disorder can be tested using various animal models known in the art. For example: efficacy in treating, preventing and/or managing asthma can be assessed using ova induced asthma model described, for example, in Lee et al. (2006) J Allergy Clin Immunol 118(2):403-9; efficacy in treating, preventing and/or managing arthritis (*e.g.,* rheumatoid or psoriatic arthritis) can be assessed using autoimmune animal models described, for example, in Williams et al. (2010) Chem Biol, 17(2):123-34, WO 2009/088986, WO2009/088880, and WO 2011/008302; and efficacy in treating, preventing and/or managing fibrosis or fibrotic condition can be assessed using the unilateral ureteral obstruction model of renal fibrosis (*see* Chevalier et al., Kidney International (2009) 75:1145-1152), the bleomycin induced model of pulmonary fibrosis (*see* Moore and Hogaboam, Am. J. Physiol. Lung. Cell. Mol. Physiol. (2008) 294:L152-L160), a variety of liver/biliary fibrosis models (*see* Chuang et al., Clin Liver Dis (2008) 12:333-347 and Omenetti, A. et al. (2007) Laboratory Investigation 87:499-514 (biliary duct-ligated model)), or a number of myelofibrosis mouse models *(see* Varicchio, L. et al. (2009) Expert Rev. Hematol. 2(3):315-334).

[0314] The present disclosure relates to 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 disclosed 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.

[0315] Also disclosed herein is a method of treating, preventing and/or managing arthritis. As used herein, "arthritis" encompasses all types and manifestations of arthritis. Examples include, but are not limited to, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis. The disease or disorder may be rheumatoid arthritis. The disease or disorder may be psoriatic arthritis. Also disclosed herein is a method of treating, preventing and/or managing one or more symptoms associated with arthritis. Examples of the symptoms include, but are not limited to, joint pain, which progresses into joint deformation, or damages in body organs such as in blood vessels, heart, lungs, skin, and muscles.

[0316] A symptom associated with the disease or disorder disclosed herein may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the pre-treatment level in the sample or subject treated, or it can be the level in a control population (*e.g.,* the level in subjects who do not have the disease or disorder or the level in samples derived from subjects who do not have the disease or disorder). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

Combination Therapy

[0317] The present disclosure also relates to methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in

combination with a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof. Such therapy may include, but is not limited to, the combination of the subject compound with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[0318] By "in combination with," it is not intended to imply that the other therapy and the PI3K modulator must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of this disclosure. The compound provided herein can be administered concurrently with, prior to (*e.g., 5* minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks before), or subsequent to (*e.g.,* 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks after), one or more other therapies (*e.g.*, one or more other additional agents). In general, each therapeutic agent will be administered at a dose and/or on a time schedule determined for that particular agent. The other therapeutic agent can be administered with the compound provided herein in a single composition or separately in a different composition. Triple therapy is also contemplated herein.

[0319] In general, it is expected that additional therapeutic agents employed in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[0320] The compound provided herein may be a first line treatment for cancer or hematologic malignancy, *i.e.,* it may be used in a subject who has not been previously administered another drug or therapy intended to treat cancer or hematologic malignancy or one or more symptoms thereof.

[0321] The compound provided herein may be a second line treatment for cancer or hematologic malignancy, *i.e.,* it may be used in a subject who has been previously administered another drug or therapy intended to treat cancer or hematologic malignancy or one or more symptoms thereof.

[0322] The compound provided herein may be a third or fourth line treatment for cancer or hematologic malignancy, *i.e.,* it may be used in a subject who has been previously administered two or three other drugs or therapies intended to treat cancer or hematologic malignancy or one or more symptoms thereof.

[0323] Where two agents are administered, the agents can be administered in any order. For example, the two agents can be administered concurrently (*i.e.,* essentially at the same time, or within the same treatment) or sequentially (*i.e.,* one immediately following the other, or alternatively, with a gap in between administration of the two). The compound provided herein may be administered sequentially (*i.e.,* after the first therapeutic).

[0324] A compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Such combination can reduce the undesired effect of high level of IgE associated with the use of one or more PI3K-δ inhibitors, if such effect occurs. This can be particularly useful in treatment of autoimmune and inflammatory disorders (AIID) such as rheumatoid arthritis. Additionally, the administration of PI3K-δ, PI3K-γ, or PI3K-δ/γ inhibitors as provided herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway.

[0325] Also disclosed herein is a combination treatment of a disease associated with PI3K-δ comprising administering to a subject in need thereof a PI3K-δ inhibitor and an agent that inhibits IgE production or activity. Other exemplary PI3K-δ inhibitors are applicable for this combination and they are described in, *e.g.,* US Pat. No. 6,800,620. Such combination treatment is particularly useful for treating autoimmune and inflammatory diseases (AIID) including, but not limited to rheumatoid arthritis.

[0326] Agents that inhibit IgE production are known in the art and they include, but are not limited to, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.,* rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

[0327] For treatment of autoimmune diseases, a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be used in combination with commonly prescribed drugs including, but not limited to, Enbrel®, Remicade®, Humira®, Avonex®, and Rebif®. For treatment of respiratory diseases, the subject compounds, or pharmaceutically acceptable forms thereof, or pharmaceutical compositions, can be administered in combination with commonly prescribed drugs including, but not limited to, Xolair®, Advair®, Singulair®, and Spiriva®.

[0328] The compounds as provided herein, or pharmaceutically acceptable forms (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be formulated or administered in conjunction with other agents that act to relieve the symptoms of inflammatory conditions such as encephalomyelitis, asthma, and the other diseases described herein. These agents

include non-steroidal anti-inflammatory drugs (NSAIDs), *e.g.*, acetylsalicylic acid; ibuprofen; naproxen; indomethacin; nabumetone; tolmetin; etc. Corticosteroids are used to reduce inflammation and suppress activity of the immune system. An exemplary drug of this type is Prednisone. Chloroquine (Aralen) or hydroxychloroquine (Plaquenil) can also be used in some individuals with lupus. They can be prescribed for skin and joint symptoms of lupus. Azathioprine (Imuran) and cyclophosphamide (Cytoxan) suppress inflammation and tend to suppress the immune system. Other agents, *e.g.*, methotrexate and cyclosporin are used to control the symptoms of lupus. Anticoagulants are employed to prevent blood from clotting rapidly. They range from aspirin at very low dose which prevents platelets from sticking, to heparin/coumadin. Other compounds used in the treatment of lupus include belimumab (Benlysta®).

[0329] A pharmaceutical composition for inhibiting abnormal cell growth in a subject may comprise an amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, in combination with an amount of an anti-cancer agent (*e.g.,* a chemotherapeutic agent). Many chemotherapeutics are presently known in the art and can be used in combination with a compound provided herein.

[0330] The chemotherapeutic may be selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (imatinib mesylate), Velcade® (bortezomib), Casodex™ (bicalutamide), Iressa® (gefitinib), Tarceva® (erlotinib), and Adriamycin® (doxorubicin) as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; BTK inhibitors such as ibrutinib (PCI-32765), AVL-292, Dasatinib, LFM-AI3, ONO-WG-307, and GDC-0834; HDAC inhibitors such as vorinostat, romidepsin, panobinostat, valproic acid, belinostat, mocetinostat, abrexinostat, entinostat, SB939, resminostat, givinostat, CUDC-101, AR-42, CHR-2845, CHR-3996, 4SC-202, CG200745, ACY-1215 and kevetrin; EZH2 inhibitors such as, but not limited to, EPZ-6438 (N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1-biphenyl]-3-carboxamide), GSK-126 ((S)-1-(sec-butyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3 -yl)methyl)-3 -methyl-6-(6-(piperazin-1-yl)pyridin-3 -yl)-1H-indole-4-carboxamide), GSK-343 (1-Isopropyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3 -yl)methyl)-6-(2-(4-methylpiperazin-1-yl)pyridine-4-yl)-1H-indazole-4-carboxamide), EI1, 3-deazaneplanocin A (DNNep, 5R-(4-amino-1H-imidazo[4,5-c]pyridin-1-yl)-3-(hydroxymethyl)-3-cyclopentene-1S,2R-diol), small interfering RNA (siRNA) duplexes targeted against EZH2 (S. M. Elbashir et al., Nature 411:494-498 (2001)), isoliquiritigenin, and those provided in, for example, U.S. Publication Nos. 2009/0012031, 2009/0203010, 2010/0222420, 2011/0251216, 2011/0286990, 2012/0014962, 2012/0071418, 2013/0040906, and 2013/0195843; JAK/STAT inhibitors such as lestaurtinib, tofacitinib, ruxolitinib, pacritinib, CYT387, baricitinib, GLPG0636, TG101348, INCB16562, CP-690550, and AZD1480; PKC-β inhibitor such as Enzastaurin; SYK inhibitors such as, but not limited to, GS-9973, R788 (fostamatinib), PRT 062607, R406, (S)-2-(2-((3,5-dimethylphenyl)amino)pyrimidin-4-yl)-N-(1-hydroxypropan-2-yl)-4-methylthiazole-5-carboxamide, R112, GSK143, BAY61-3606, PP2, PRT 060318, R348, and those provided in, for example, U.S. Publication Nos. 2003/0113828, 2003/0158195, 2003/0229090, 2005/0075306, 2005/0232969, 2005/0267059, 2006/0205731, 2006/0247262, 2007/0219152, 2007/0219195, 2008/0114024, 2009/0171089, 2009/0306214, 2010/0048567, 2010/0152159, 2010/0152182, 2010/0316649, 2011/0053897, 2011/0112098, 2011/0245205, 2011/0275655, 2012/0027834, 2012/0093913, 2012/0101275, 2012/0130073, 2012/0142671, 2012/0184526, 2012/0220582, 2012/0277192, 2012/0309735, 2013/0040984, 2013/0090309, 2013/0116260, and 2013/0165431; SYK/JAK dual inhibitor such as PRT2070; nitrogen mustards such as bendamustine, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomycins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pralatrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatrexate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid;

2-ethylhydrazide; procarbazine; PSK.R™; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethyla- mine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (Ara-C); cyclophosphamide; thiotepa; taxanes, *e.g.,* paclitaxel (*e.g.,* TAXOL™) and docetaxel (*e.g.,* TAXOTERE™) and ABRAXANE® (paclitaxel protein-bound particles); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable forms (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical composition as provided herein can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, abagovomab, acridine carboxamide, adecatumumab, 17-N-allylamino-17-demethoxygeldanamycin, alpharadin, alvocidib, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, amonafide, anthracenedione, anti-CD22 immunotoxins, antineoplastic, antitumorigenic herbs, apaziquone, atiprimod, azathioprine, belotecan, bendamustine, BIBW 2992, biricodar, brostallicin, bryostatin, buthionine sulfoximine, CBV (chemotherapy), calyculin, crizotinib, cell-cycle nonspecific antineoplastic agents, dichloroacetic acid, discodermolide, elsamitrucin, enocitabine, epothilone, eribulin, everolimus, exatecan, exisulind, ferruginol, forodesine, fosfestrol, ICE chemotherapy regimen, IT-101, imexon, imiquimod, indolocarbazole, irofulven, laniquidar, larotaxel, lenalidomide, lucanthone, lurtotecan, mafosfamide, mitozolomide, nafoxidine, nedaplatin, olaparib, ortataxel, PAC-1, pawpaw, pixantrone, proteasome inhibitor, rebeccamycin, resiquimod, rubitecan, SN-38, salinosporamide A, sapacitabine, Stanford V, swainsonine, talaporfin, tariquidar, tegafur-uracil, temodar, tesetaxel, triplatin tetranitrate, tris(2-chloroethyl)amine, troxacitabine, uramustine, vadimezan, vinflunine, ZD6126, and zosuquidar.

[0331] The chemotherapeutic may be selected from hedgehog inhibitors including, but not limited to IPI-926 (*See* U.S. Patent 7,812,164). Other suitable hedgehog inhibitors include, for example, those described and disclosed in U.S. Patent 7,230,004, U.S. Patent Application Publication No. 2008/0293754, U.S. Patent Application Publication No. 2008/0287420, and U.S. Patent Application Publication No. 2008/0293755. Examples of other suitable hedgehog inhibitors include those described in U.S. Patent Application Publication Nos. US 2002/0006931, US 2007/0021493 and US 2007/0060546, and International Application Publication Nos. WO 2001/19800, WO 2001/26644, WO 2001/27135, WO 2001/49279, WO 2001/74344, WO 2003/011219, WO 2003/088970, WO 2004/020599, WO 2005/013800, WO 2005/033288, WO 2005/032343, WO 2005/042700, WO 2006/028958, WO 2006/050351, WO 2006/078283, WO 2007/054623, WO 2007/059157, WO 2007/120827, WO 2007/131201, WO 2008/070357, WO 2008/110611, WO 2008/112913, and WO 2008/131354. Additional examples of hedgehog inhibitors include, but are not limited to, GDC-0449 (also known as RG3616 or vismodegib) described in, *e.g.,* Von Hoff D. et al., N. Engl. J. Med. 2009; 361(12):1164-72; Robarge K.D. et al., Bioorg Med Chem Lett. 2009; 19(19):5576-81; Yauch, R. L. et al. (2009) Science 326: 572-574; Sciencexpress: 1-3 (10.1126/science.1179386); Rudin, C. et al. (2009) New England J of Medicine 361-366 (10.1056/nejma0902903); BMS-833923 (also known as XL139) described in, *e.g.,* in Siu L. et al., J. Clin. Oncol. 2010; 28:15s (suppl; abstr 2501); and National Institute of Health Clinical Trial Identifier No. NCT006701891; LDE-225 described, *e.g.,* in Pan S. et al., ACS Med. Chem. Lett., 2010; 1(3): 130-134; LEQ-506 described, *e.g.,* in National Institute of Health Clinical Trial Identifier No. NCT01106508; PF-04449913 described, *e.g.,* in National Institute of Health Clinical Trial Identifier No. NCT00953758; Hedgehog pathway antagonists disclosed in U.S. Patent Application Publication No. 2010/0286114; SMOi2-17 described, *e.g.,* U.S. Patent Application Publication No. 2010/0093625; SANT-1 and SANT-2 described, *e.g.,* in Rominger C.M. et al., J. Pharmacol. Exp. Ther. 2009; 329(3):995-1005; 1-piperazinyl-4-arylphthalazines or analogues thereof, described in Lucas B.S. et al., Bioorg. Med. Chem. Lett. 2010; 20(12):3618-22.

[0332] Other hormonal therapy and chemotherapeutic agents include, but are not limited to, anti-estrogens (*e.g.* tamoxifen, raloxifene, and megestrol acetate), LHRH agonists (*e.g.* goserelin and leuprolide), anti-androgens (*e.g.* flutamide and bicalutamide), photodynamic therapies (*e.g.* vertoporfin (BPD-MA), phthalocyanine, photosensitizer Pc4, and demethoxy-hypocrellin A (2BA-2-DMHA)), nitrogen mustards (*e.g.* cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (*e.g.* carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (*e.g.* busulfan and treosulfan), triazenes (*e.g.* dacarbazine, temozolomide), platinum containing compounds (*e.g.* cisplatin, carboplatin, oxaliplatin), vinca alkaloids (*e.g.* vincristine, vinblastine, vindesine, and vinorelbine), taxoids or taxanes (*e.g.* paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (Abraxane), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and glucose-conjugated paclitaxel, *e.g.,* 2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (*e.g.* etoposide, etoposide phos-

phate, teniposide, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C), anti-metabolites, DHFR inhibitors (*e.g.* methotrexate, dichloromethotrexate, trimetrexate, edatrexate), IMP dehydrogenase inhibitors (*e.g.* mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonuclotide reductase inhibitors (*e.g.* hydroxyurea and deferoxamine), uracil analogs (*e.g.* 5-fluorouracil (5-FU), floxuridine, doxifluridine, raltitrexed, tegafur-uracil, capecitabine), cytosine analogs (*e.g.* cytarabine (ara C, cytosine arabinoside), and fludarabine), purine analogs (*e.g.* mercaptopurine and thioguanine), Vitamin D3 analogs (*e.g.* EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (*e.g.* lovastatin), dopaminergic neurotoxins (*e.g.* 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (*e.g.* staurosporine), actinomycin (*e.g.* actinomycin D, dactinomycin), bleomycin (*e.g.* bleomycin A2, bleomycin B2, peplomycin), anthracyclines (*e.g.* daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (*e.g.* verapamil), Ca2+ ATPase inhibitors (*e.g.* thapsigargin), thalidomide, lenalidomide (REVLIMID®), tyrosine kinase inhibitors (*e.g.*, axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTINTM, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTTN®), bevacizumab (AVASTTN®), rituximab (RTTUXAN®), cetuximab (ERBTTUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), sorafenib (NEXAVAR®), everolimus (AFINITOR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), temsirolimus (TORISEL®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW2992 (TOVOKTM), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (*e.g.,* bortezomib (Velcade)), mTOR inhibitors (*e.g.,* rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbazine, prednisolone, dexamethasone, camptothecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin,, aminopterin, and hexamethyl melamine.

[0333] Exemplary biotherapeutic agents include, but are not limited to, interferons, cytokines (*e.g.*, tumor necrosis factor, interferon α, interferon γ), vaccines, hematopoietic growth factors, monoclonal serotherapy, immunostimulants and/or immuno-modulatory agents (*e.g.,* IL-1, 2, 4, 6, or 12), immune cell growth factors (*e.g.,* GM-CSF) and antibodies (*e.g.* Herceptin (trastuzumab), T-DM1, AVASTIN (bevacizumab), ERBITUX (cetuximab), Vectibix (panitumumab), Rituxan (rituximab), Bexxar (tositumomab), or Perjeta (pertuzumab)).

[0334] The biotherapeutic agent may be an anti-CD37 antobody such as, but not limited to, IMGN529, K7153A and TRU-016. The biotherapeutic agent may be an anti-CD20 antibody such as, but not limited to, ^{131}I tositumomab, ^{90}Y ibritumomab, ^{111}I ibritumomab, obinutuzumab and ofatumumab. The biotherapeutic agent may be an anti-CD52 antibody such as, but not limited to, alemtuzumab.

[0335] The chemotherapeutic may be selected from HSP90 inhibitors. The HSP90 inhibitor can be a geldanamycin derivative, *e.g.,* a benzoquinone or hygroquinone ansamycin HSP90 inhibitor (*e.g.,* IPI-493 and/or IPI-504). Non-limiting examples of HSP90 inhibitors include IPI-493, IPI-504, 17-AAG (also known as tanespimycin or CNF-1010), BIIB-021 (CNF-2024), BIIB-028, AUY-922 (also known as VER-49009), SNX-5422, STA-9090, AT-13387, XL-888, MPC-3100, CU-0305, 17-DMAG, CNF-1010, Macbecin (*e.g.,* Macbecin I, Macbecin II), CCT-018159, CCT-129397, PU-H71, or PF-04928473 (SNX-2112).

[0336] The chemotherapeutic may be selected from PI3K inhibitors (*e.g.,* including those PI3K inhibitors provided herein and those PI3K inhibitors not provided herein). The PI3K inhibitor may be an inhibitor of delta and gamma isoforms of PI3K. The PI3K inhibitor may be an inhibitor of delta isoform of PI3K. The PI3K inhibitor may be an inhibitor of gamma isoform of PI3KThe PI3K inhibitor may be an inhibitor of alpha isoform of PI3K. The PI3K inhibitor may be an inhibitor of one or more alpha, beta, delta and gamma isoforms of PI3K. Exemplary PI3K inhibitors that can be used in combination are described in, *e.g.,* WO 09/088990, WO 09/088086, WO 2011/008302, WO 2010/036380, WO 2010/006086, WO 09/114870, WO 05/113556; US 2009/0312310, and US 2011/0046165. Additional PI3K inhibitors that can be used in combination with the pharmaceutical compositions, include but are not limited to, AMG-319, GSK 2126458, GDC-0980, GDC-0941, Sanofi XL147, XL499, XL756, XL147, PF-4691502, BKM 120, CAL-101 (GS-1101), CAL 263, SF1126, PX-886, and a dual PI3K inhibitor (*e.g.,* Novartis BEZ235). The PI3K inhibitor may be an isoquinolinone.

[0337] The PI3K gamma selective compound may selectively inhibit PI3K gamma isoform over PI3K delta isoform. The PI3K gamma selective compound may have a delta/gamma selectivity ratio of greater than 1, greater than about 5, greater than about 10, greater than about 50, greater than about 100, greater than about 200, greater than about 400, greater than about 600, greater than about 800, greater than about 1000, greater than about 1500, greater than about 2000, greater than about 5000, greater than about 10,000, or greater than about 20,000. The PI3K gamma selective compound may have a delta/gamma selectivity ratio in the range of from greater than 1 to about 5, from about 5 to about

10, from about 10 to about 50, from about 50 to about 850, or greater than about 850. The delta/gamma selectivity ratio may be determined by dividing the compound's IC_{50} against PI3K delta isoform by the compound's IC_{50} against PI3K gamma isoform.

[0338] For example, a compound provided herein with a delta/gamma selectivity ratio of greater than 150 can be combined with a compound that has a gamma/delta selectivity ratio of 1000 at various amounts (*e.g.,* a ratio of 10:1 or 40:1 of a gamma selective compound and a delta selective compound) to provide synergistic effect in cell lines (*e.g.,* diffuse large B-celllymphoma cell lines such as SU-DHL-4).

[0339] The present disclosure also relates to a method for using a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, in combination with radiation therapy in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the subject. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of a compound provided herein in this combination therapy can be determined as described herein.

[0340] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation, external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (*e.g.,* At-211, 1-131, 1-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner as provided herein include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, 1-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), *e.g.,* a solution of 1-125 or 1-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

[0341] Without being limited by any theory, a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, disclosed herein is a method for sensitizing abnormal cells in a subject to treatment with radiation which comprises administering to the subject an amount of a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound used in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

[0342] A compound as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

[0343] Other therapeutic agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound provided herein, or a pharmaceutically acceptable form thereof, or a pharmaceutical composition described herein. Such therapeutic agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931, 788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997). In some embodiments, MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. Other embodiments include those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (*e.g.,* MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some non-limiting examples of MMP inhibitors are AG-3340, RO 32-3555, and RS 13-0830.

[0344] Autophagy inhibitors include, but are not limited to, chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNAs that inhibit expression of proteins including, but not limited to ATG5 (which are implicated in autophagy), can also be used.

[0345] The present disclosure also relates to a method of and/or a pharmaceutical composition for treating a cardiovascular disease in a subject which comprises an amount of a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, and an amount of one or more therapeutic agents use for the treatment of cardiovascular diseases.

[0346] Exemplary agents for use in cardiovascular disease applications are anti-thrombotic agents, *e.g.,* prostacyclin and salicylates, thrombolytic agents, *e.g.,* streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), anti-platelets agents, *e.g.,* acetyl-salicylic acid (ASA) and clopidrogel, vasodilating agents, *e.g.,* nitrates, calcium channel blocking drugs, anti-proliferative agents, *e.g.,* colchicine and alkylating agents, intercalating agents, growth modulating factors such as interleukins, transformation growth factor-beta and congeners of platelet derived growth factor, monoclonal antibodies directed against growth factors, anti-inflammatory agents, both steroidal and non-steroidal, and other agents that can modulate vessel tone, function, arteriosclerosis, and the healing response to vessel or organ injury post intervention. Antibiotics can also be included in combinations or coatings. Moreover, a coating can be used to effect therapeutic delivery focally within the vessel wall. By incorporation of the active agent in a swellable polymer, the active agent will be released upon swelling of the polymer.

[0347] Acompound provided herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, can be formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm, interceed and hyaluronic acid.

[0348] Medicaments which can be administered in conjunction with a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, include any suitable drugs usefully delivered by inhalation for example, analgesics, *e.g.,* codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, *e.g.,* diltiazem; antiallergics, *e.g.* cromoglycate, ketotifen or nedocromil; anti-infectives, *e.g.,* cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, *e.g.,* methapyrilene; anti-inflammatories, *e.g.,* beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, *e.g.,* noscapine; bronchodilators, *e.g.,* ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, *e.g.,* amiloride; anticholinergics *e.g.,* ipratropium, atropine or oxitropium; hormones, *e.g.,* cortisone, hydrocortisone or prednisolone; xanthines *e.g.,* aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, *e.g.,* insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments can be used in the form of salts (*e.g.,* as alkali metal or amine salts or as acid addition salts) or as esters (*e.g.,* lower alkyl esters) to optimize the activity and/or stability of the medicament.

[0349] Other exemplary therapeutic agents useful for a combination therapy include, but are not limited to, agents as described above, radiation therapy, hormone antagonists, hormones and their releasing factors, thyroid and antithyroid drugs, estrogens and progestins, androgens, adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones, insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas, agents affecting calcification and bone turnover: calcium, phosphate, parathyroid hormone, vitamin D, calcitonin, vitamins such as water-soluble vitamins, vitamin B complex, ascorbic acid, fat-soluble vitamins, vitamins A, K, and E, growth factors, cytokines, chemokines, muscarinic receptor agonists and antagonists; anticholinesterase agents; agents acting at the neuromuscular junction and/or autonomic ganglia; catecholamines, sympathomimetic drugs, and adrenergic receptor agonists or antagonists; and 5-hydroxytryptamine (5-HT, serotonin) receptor agonists and antagonists.

[0350] Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[0351] Additional therapeutic agents contemplated herein include diuretics, vasopressin, agents affecting the renal conservation of water, rennin, angiotensin, agents useful in the treatment of myocardial ischemia, anti-hypertensive agents, angiotensin converting enzyme inhibitors, β-adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

[0352] Other therapeutic agents contemplated herein include drugs used for control of gastric acidity, agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease. Therapeutic agents include, but are not limited to, those used to treat protozoan infections, drugs used to treat Malaria, Amebiasis, Giardiasis, Trichomoniasis, Trypanosomiasis, and/or Leishmaniasis, and/or drugs used in the chemotherapy of helminthiasis. Other therapeutic agents include, but are not limited to, antimicrobial agents, sulfonamides, trimethoprim-sulfamethoxazole quinolones, and agents for urinary tract infections, penicillins, cephalosporins, and other, β-Lactam antibiotics, an agent containing an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy, antifungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

[0353] Examples of therapeutic antibodies that can be combined with a compound provided herein include but are not limited to anti-receptor tyrosine kinase antibodies (cetuximab, panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

[0354] Moreover, therapeutic agents used for immuno-modulation, such as immuno-modulators, immunosuppressive agents, tolerogens, and immunostimulants are contemplated by the methods herein. In addition, therapeutic agents acting on the blood and the blood-forming organs, hematopoietic agents, growth factors, minerals, and vitamins, anticoagulant, thrombolytic, and anti-platelet drugs are also contemplated by the methods herein.

[0355] In exemplary embodiments, for treating renal carcinoma, one can combine a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, and isotopically labeled derivatives) thereof, or a pharmaceutical composition as provided herein, with sorafenib and/or avastin. For treating an endometrial disorder, one can combine a compound provided herein with doxorubicin, taxotere (taxol), and/or cisplatin (carboplatin). For treating ovarian cancer, one can combine a compound provided herein with cisplatin, carboplatin, docetaxel, doxorubincin, topotecan, and/or tamoxifen. For treating breast cancer, one can combine a compound provided herein with paclitaxel or docetaxel, gemcitabine, capecitabine, tamoxifen, letrozole, erlotinib, lapatinib, PD0325901, bevacizumab, trastuzumab, OSI-906, and/or OSI-930. For treating lung cancer, one can combine a compound as provided herein with paclitaxel, docetaxel, gemcitabine, cisplatin, pemetrexed, erlotinib, PD0325901, and/or bevacizumab.

[0356] The disorder to be treated, prevented and/or managed may be a hematological cancer, *e.g.,* lymphoma (*e.g.,* T-cell lymphoma; NHL), myeloma (*e.g.,* multiple myeloma), and leukemia (*e.g.,* CLL), and a compound provided herein may be used in combination with: HDAC inhibitors such as vorinostat, romidepsin and ACY-1215; mTOR inhibitors such as everolimus; anti-folates such as pralatrexate; nitrogen mustard such as bendamustine; gemcitabine, optionally in further combination with oxaliplatin; rituximab-cyclophosphamide combination; PI3K inhibitors such as GS-1101, XL 499, GDC-0941, and AMG-319; angiogenesis inhibitors such as pomalidomide or BTK inhibitors such as ibrutinib, AVL-292, Dasatinib, LFM-AI3, ONO-WG-307, and GDC-0834. The disorder to be treated, prevented and/or managed may be DLBCL, and a compound provided herein (*e.g.*,compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, is used in combination with HDAC inhibitors provided herein. The HDAC inhibitor may be ACY-1215.

[0357] The disorder to be treated, prevented and/or managed may be DLBCL, and a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.*, salt or solvate) thereof, may be used in combination with BTK inhibitors provided herein. The BTK inhibitor may be ibmtinib. The BTK inhibitor may be AVL-292.

[0358] The disorder to be treated, prevented and/or managed may be DLBCL, and a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, maybe used in combination with IRAK inhibitors provided herein. The IRAK4 inhibitor may be ND-2110 or ND-2158.

[0359] The disorder to be treated, prevented and/or managed may be WM, and a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination with BTK inhibitors provided herein. The BTK inhibitor may be ibmtinib. The BTK inhibitor may be AVL-292.

[0360] The disorder to be treated, prevented and/or managed may be WM, and a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination with IRAK4 inhibitors provided herein. The IRAK4 inhibitor may be ND-2110 or ND-2158.

[0361] The disorder to be treated, prevented and/or managed may be T-ALL, the subject/patient may have a PTEN deficiency, and a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination with doxorubicin and/or vincristine.

[0362] When inflammation (*e.g.,* arthritis, asthma) is treated, prevented and/or managed, a compound provided herein can be combined with, for example: PI3K inhibitors such as GS-1101, XL 499, GDC-0941, and AMG-319; BTK inhibitors such as ibrutinib and AVL-292; JAK inhibitors such as tofacitinib, fostamatinib, and GLPG0636.

[0363] When asthma is treated, prevented and/or managed, a compound provided herein can be combined with, for example: beta 2-agonists such as, but not limited to, albuterol (Proventil®, or Ventolin®), salmeterol (Serevent®), formoterol (Foradil®), metaproterenol (Alupent®), pirbuterol (MaxAir®), and terbutaline sulfate; corticosteroids such as, but not limited to, budesonide (*e.g.,* Pulmicort®), flunisolide (*e.g.,* AeroBid Oral Aerosol Inhaler® or Nasalide Nasal Aerosol®), fluticasone (*e.g.,* Flonase® or Flovent®) and triamcinolone (*e.g.,* Azmacort®); mast cell stabilizers such as cromolyn sodium (*e.g.,* Intal® or Nasalcrom®) and nedocromil (*e.g.,* Tilade®); xanthine derivatives such as, but not limited to, theophylline (*e.g.,* Aminophyllin®, Theo-24® or Theolair®); leukotriene receptor antagonists such as, but are not limited to, zafirlukast (Accolate®), montelukast (Singulair®), and zileuton (Zyflo®); and adrenergic agonists such as, but are not limited to, epinephrine (Adrenalin®, Bronitin®, EpiPen® or Primatene Mist®).

[0364] When arthritis is treated, prevented and/or managed, a compound provided herein can be combined with, for example: TNF antagonist (*e.g.,* a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist); other biologic antirhheumatics (*e.g.,* IL-6 antagonists, IL-1 antagonists, costimulatory modulators); an antirheumatic (*e.g.,* methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, chrloroquine, hydroxychloroquine sulfate, leflunomide, sulfasalzine, penicillamine); a muscle relaxant; a narcotic; a non-steroid anti-inflammatory drug (NSAID); an analgesic; an anesthetic; a sedative; a local anesthetic; a neuromuscular blocker; an antimicrobial (*e.g.,* an aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluoroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial); an antipsoriatic; a corticosteroid; an anabolic steroid; a cytokine or a cytokine antagonist; a calcineurin inhibitor (*e.g.,* cyclosporine, tacrolimus).

[0365] A compound provided herein (*e.g.,* a compound of Formula I (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) may be administered in combination with an agent for the treatment of rheumatoid arthritis. Examples of agents for the treatment of rheumatoid arthritis include, but are not limited to, various NSAIDs, corticosteroids, sulfasalazine, auranofin, methotrexate, azathioprine, penicillamine, cyclosporine, Arava (leflunomide), TNF inhibitors (*e.g.,* Enbrel (etanercept), Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), and Cimzia (certolizumab)), IL-1 inhibitors (*e.g.,* Kineret (anakinra)), T-cell costimulatory modulators (*e.g.,* Orencia (abatacept)), Anti-CD20 (*e.g.,* Rituxan (rituximab)), and IL-6 inhibitors (*e.g.,* Actemra (tocilizumab)). The agent may be Cimzia (certolizumab). The agent may be Actemra (tocilizumab).

[0366] A compound provided herein (*e.g.,* a compound of Formula I (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) may be administered in combination with an agent for rheumatology. Examples of agents for rheumatology include, but are not limited to, Rayos (prednisone), Stendra (avanafil), Actemra (tocilizumab), Duexis (ibuprofen and famotidine), Actemra (tocilizumab), Krystexxa (pegloticase), Vimovo (naproxen + esomeprazole), Cimzia (certolizumab pegol), Colcrys (colchicine), Pennsaid (diclofenac sodium topical solution), Simponi (golimumab), Uloric (febuxostat), Orencia (abatacept), Elaprase (idursulfase), Orencia (abatacept), Vioxx (rofecoxib), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Bextra, Kineret, Remicade (infliximab), Supartz, Mobic (meloxicam), Vivelle (estradiol transdermal system), Lodine XL (etodolac), Arava, Salagen, Arthrotec, Etodolac, Ketoprofen, Synvisc, Tolmetin Sodium, Azulfidine EN-tabs Tablets (sulfasalazine delayed release tablets, USP), and Naprelan (naproxen sodium).

[0367] The second agent may be selected from belimumab, AGS-009, rontalizumab, vitamin D3, sifalimumab, AMG 811, IFNα Kinoid, CEP33457, epratuzumab, LY2127399, Ocrelizumab, Atacicept, A-623, SBI-087, AMG557, laquinimod, rapamycin, cyclophosphamide, azathioprine, mycophenolate, leflunomide, methotrexate, CNTO 136, tamibarotene, N-acetylcysteine, CDP7657, hydroxychloroquine, rituximab, carfilzomib, bortezomib, ONX 0914, IMO-3100, DV1179, sulfasalazine, and chloroquine. The second agent may be methotrexate, sulfasalazine, chloroquine, or hydroxychloroquine. The second agent may be methotrexate.

[0368] When cystic fibrosis is treated, prevented and/or managed, a compound provided herein can be combined with, for example, 552-02, 5-methyltetrahydrofolate and vitamin B12, Ad5-CB-CFTR, Adeno-associated virus-CFTR vector, albuterol, alendronate, alpha tocopherol plus ascorbic acid, amiloride HCl, aquADEKTM, ataluren (PTC124), AZD1236, AZD9668, azithromycin, bevacizumab, biaxin (clarithromycin), BIIL 283 BS (amelubent), buprofen, calcium carbonate, ceftazidime, cholecalciferol, choline supplementation, CPX, cystic fibrosis transmembrane conductance reg-

ulator, DHA-rich supplement, digitoxin, cocosahexaenoic acid (DHA), doxycycline, ECGC, ecombinant human IGF-1, educed glutathione sodium salt, ergocalciferol (vitamin D2), fluorometholone, gadobutrol (GADOVIST®, BAY86-4875), gentamicin, ghrelin, glargine, glutamine, growth hormone, GS-9411, H5.001CBCFTR, human recombinant growth hormone, hydroxychloroquine, hyperbaric oxygen, hypertonic saline, IH636 grape seed proanthocyanidin extract, insulin, interferon gamma-lb, IoGen (molecular iodine), iosartan potassium, isotonic saline, itraconazole, IV gallium nitrate (GANITE®) infusion, ketorolac acetate, lansoprazole, L-arginine, linezolid, lubiprostone, meropenem, miglustat, MP-376 (levofloxacin solution for inhalation), normal saline IV, Nutropin AQ, omega-3 triglycerides, pGM169/GL67A, pGT-1 gene lipid complex, pioglitazone, PTC124, QAU145, salmeterol, SB656933, SB656933, simvastatin, sitagliptin, sodium 4-phenylbutyrate, standardized turmeric root extract, tgAAVCF, TNF blocker, TOBI, tobramycin, tocotrienol, unconjugated Isoflavones 100, vitamin: choline bitartrate (2-hydroxyethyl) trimethylammonium salt 1:1, VX-770, VX-809, Zinc acetate, or combinations thereof.

[0369] A compound provided herein may be administered in combination with an agent that inhibits IgE production or activity. The PI3K inhibitor (*e.g.,* PI3Kδ inhibitor) may be administered in combination with an inhibitor of mTOR. Agents that inhibit IgE production are known in the art and they include but are not limited to one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.* rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

[0370] Further therapeutic agents that can be combined with a compound provided herein can be found in Goodman and Gilman's "The Pharmacological Basis of Therapeutics" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference.

[0371] The compounds described herein can be used in combination with the agents provided herein or other suitable agents, depending on the condition being treated. Hence, a compound provided herein, or a pharmaceutically acceptable form thereof, may be be co-administered with other agents as described above. When used in combination therapy, a compound described herein, or a pharmaceutically acceptable form thereof, can be administered with a second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound provided herein and any of the agents described above can be simultaneously administered, wherein both agents are present in separate formulations. In another alternative, a compound provided herein can be administered just followed by any of the agents described above, or vice versa. In the separate administration protocol, a compound provided herein and any of the agents described above can be administered a few minutes apart, or a few hours apart, or a few days apart.

[0372] Administration of a compound provided herein, or a pharmaceutically acceptable form thereof, can be effected by any method that enables delivery of the compound to the site of action. An effective amount of a compound provided herein, or a pharmaceutically acceptable form thereof, can 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, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[0373] When a compound provided herein, or a pharmaceutically acceptable form thereof, is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound provided herein, unit dose forms of the agent and the compound as provided herein can be adjusted accordingly.

[0374] The compound provided herein and the second agent may be administered as separate compositions, *e.g.,* pharmaceutical compositions. The PI3K modulator and the agent may be administered separately, but via the same route (*e.g.,* both orally or both intravenously). The PI3K modulator and the agent may be administered in the same composition, *e.g.,* pharmaceutical composition.

[0375] A compound provided herein (*e.g.,* a compound of Formula I (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) may be administered in combination with an agent for pulmonary or respiratory diseases. Examples of agents for pulmonary or respiratory diseases include, but are not limited to, Dymista (azelastine hydrochloride and fluticasone propionate), Kalydeco (ivacaftor), Qnasl (beclomethasone dipropionate) nasal aerosol, Rayos (prednisone) delayed-release tablets, Surfaxin (lucinactant), Tudorza Pressair (aclidinium bromide inhalation powder), Arcapta (indacaterol maleate inhalation powder), Daliresp (roflumilast), Xalkori (crizotinib), Cayston (aztreonam for inhalation solution), Dulera (mometasone furoate + formoterol fumarate dihydrate), Teflaro (ceftaroline fosamil), Adcirca (tadalafil), Tyvaso (treprostinil), Alvesco (ciclesonide), Patanase (olopatadine hydrochloride), Letairis (ambrisentan), Xyzal (levocetirizine dihydrochloride), Brovana (arformoterol tartrate), Tygacil (tigecycline), Ketek (telithromycin), Spiriva HandiHaler (tiotropium bromide), Aldurazyme (laronidase), Iressa (gefitinib), Xolair (omalizumab), Zemaira (alpha1-proteinase inhibitor), Clarinex, Qvar (be-

clomethasone dipropionate), Remodulin (treprostinil), Xopenex, Avelox I.V. (moxifloxacin hydrochloride), DuoNeb (albuterol sulfate and ipratropium bromide), Foradil Aerolizer (formoterol fumarate inhalation powder), Invanz, NasalCrom Nasal Spray, Tavist (clemastine fumarate), Tracleer (bosentan), Ventolin HFA (albuterol sulfate inhalation aerosol), Biaxin XL (clarithromycin extended-release tablets), Cefazolin and Dextrose USP, Tri-Nasal Spray (triamcinolone acetonide spray), Accolate, Cafcit Injection, Proventil HFA Inhalation Aerosol, Rhinocort Aqua Nasal Spray, Tequin, Tikosyn Capsules, Allegra-D, Clemastine fumarate syrup, Curosurf, Dynabac, Infasurf, Priftin, Pulmozyme (dornase alfa), Sclerosol Intrapleural Aerosol, Singulair, Synagis, Ceftin (cefuroxime axetil), Cipro (ciprofloxacin HCl), Claritin RediTabs (10 mg loratadine rapidly-disintegrating tablet), Flonase Nasal Spray, Flovent Rotadisk, Metaprotereol Sulfate Inhalation Solution (5%), Nasacort AQ (triamcinolone acetonide) Nasal Spray, Omnicef, Raxar (grepafloxacin), Serevent, Tilade (nedocromil sodium), Tobi, Vanceril 84 mcg Double Strength (beclomethasone dipropionate, 84 mcg) Inhalation Aerosol, Zagam (sparfloxacin) tablets, Zyflo (Zileuton), Accolate, Allegra (fexofenadine hydrochloride), Astelin nasal spray, Atrovent (ipratropium bromide), Augmentin (amoxicillin/clavulanate), Azmacort (triamcinolone acetonide) Inhalation Aerosol, Breathe Right, Claritin Syrup (loratadine), Claritin-D 24 Hour Extended Release Tablets (10 mg loratadine, 240 mg pseudoephedrine sulfate), Covera-HS (verapamil), Nasacort AQ (triamcinolone acetonide) Nasal Spray, OcuHist, Pulmozyme (dornase alfa), RespiGam (Respiratory Syncitial Virus Immune Globulin Intravenous), Tavist (clemastine fumarate), Tripedia (Diptheria and Tetanus Toxoids and Acellular Pertussis Vaccine Absorbed), Vancenase AQ 84 mcg Double Strength, Visipaque (iodixanol), Zosyn (sterile piperacillin sodium/tazobactam sodium), Cedax (ceftibuten), and Zyrtec (cetirizine HCl). The agent for pulmonary or respiratory diseases may be Arcapta, Daliresp, Dulera, Alvesco, Brovana, Spiriva HandiHaler, Xolair, Qvar, Xopenex, DuoNeb, Foradil Aerolizer, Accolate, Singulair, Flovent Rotadisk, Tilade, Vanceril, Zyflo, or Azmacort Inhalation Aerosol. The agent for pulmonary or respiratory diseases may be Spiriva HandiHaler.

[0376] A compound provided herein (*e.g.,* a compound of Formula I (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof) may be administered in combination with an agent for immunology or infectious diseases. Examples of agents for immunology or infectious diseases include, but are not limited to, Horizant (gabapentin enacarbil), Qnasl (beclomethasone dipropionate) nasal aerosol, Rayos (prednisone) delayed-release tablets, Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate), Tudorza Pressair (aclidinium bromide inhalation powder), Arcapta (indacaterol maleate inhalation powder), Benlysta (belimumab), Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate), Daliresp (roflumilast), Dificid (fidaxomicin), Edurant (rilpivirine), Firazyr (icatibant), Gralise (gabapentin), Incivek (telaprevir), Nulojix (belatacept), Victrelis (boceprevir), Cayston (aztreonam for inhalation solution), Egrifta (tesamorelin for injection), Menveo (meningitis vaccine), Oravig (miconazole), Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine), Teflaro (ceftaroline fosamil), Zortress (everolimus), Zymaxid (gatifloxacin ophthalmic solution), Bepreve (bepotastine besilate ophthalmic solution), Berinert (C1 Esterase Inhibitor (Human)), Besivance (besifloxacin ophthalmic suspension), Cervarix [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant], Coartem (artemether/lumefantrine), Hiberix (Haemophilus b Conjugate Vaccine; Tetanus Toxoid Conjugate), Ilaris (canakinumab), Ixiaro (Japanese Encephalitis Vaccine, Inactivated, Adsorbed), Kalbitor (ecallantide), Qutenza (capsaicin), Vibativ (telavancin), Zirgan (ganciclovir ophthalmic gel), Aptivus (tipranavir), Astepro (azelastine hydrochloride nasal spray), Cinryze (C1 Inhibitor (Human)), Intelence (etravirine), Moxatag (amoxicillin), Rotarix (Rotavirus Vaccine, Live, Oral), Tysabri (natalizumab), Viread (tenofovir disoproxil fumarate), Altabax (retapamulin), AzaSite (azithromycin), Doribax (doripenem), Extina (ketoconazole), Isentress (raltegravir), Selzentry (maraviroc), Veramyst (fluticasone furoate), Xyzal (levocetirizine dihydrochloride), Eraxis (anidulafungin), Gardasil (quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine), Noxafil (posaconazole), Prezista (darunavir), Rotateq (rotavirus vaccine, live oral pentavalent), Tyzeka (telbivudine), Veregen (kunecatechins), Aptivus (tipranavir), Baraclude (entecavir), Tygacil (tigecycline), Ketek (telithromycin), Tindamax, tinidazole, Xifaxan (rifaximin), Amevive (alefacept), FluMist (Influenza Virus Vaccine), Fuzeon (enfuvirtide), Lexiva (fosamprenavir calcium), Reyataz (atazanavir sulfate), Alinia (nitazoxanide), Clarinex, Daptacel, Fluzone Preservative-free, Hepsera (adefovir dipivoxil), Pediarix Vaccine, Pegasys (peginterferon alfa-2a), Restasis (cyclosporine ophthalmic emulsion), Sustiva, Vfend (voriconazole), Avelox I.V. (moxifloxacin hydrochloride), Cancidas, Peg-Intron (peginterferon alfa-2b), Rebetol (ribavirin), Spectracef, Twinrix, Valcyte (valganciclovir HCl), Viread (tenofovir disoproxil fumarate), Xigris (drotrecogin alfa [activated]), ABREVA (docosanol), Biaxin XL (clarithromycin extended-release tablets), Cefazolin and Dextrose USP, Children's Motrin Cold, Evoxac, Kaletra Capsules and Oral Solution, Lamisil (terbinafine hydrochloride) Solution (1%), Lotrisone (clotrimazole/betamethasone diproprionate) lotion, Malarone (atovaquone; proguanil hydrochloride) Tablet, Rapamune (sirolimus) Tablets, Rid Mousse, Tri-Nasal Spray (triamcinolone acetonide spray), Trivagizole 3 (clotrimazole) Vaginal Cream, Trizivir (abacavir sulfate; lamivudine; zidovudine AZT) Tablet, Agenerase (amprenavir), Cleocin (clindamycin phosphate), Famvir (famciclovir), Norvir (ritonavir), Panretin Gel, Rapamune (sirolimus) oral solution, Relenza, Synercid I.V., Tamiflu capsule, Vistide (cidofovir), Allegra-D, CellCept, Clemastine fumarate syrup, Cleocin (clindamycin phosphate), Dynabac, REBETRON (TM) Combination Therapy, Simulect, Timentin, Viroptic, INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), Acyclovir Capsules, Aldara (im-

iquimod), Aphthasol, Combivir, Condylox Gel 0.5% (pokofilox), Famvir (famciclovir), Flagyl ER, Flonase Nasal Spray, Fortovase, INFERGEN (interferon alfacon-1), Intron A (interferon alfa-2b, recombinant), Norvir (ritonavir), Rescriptor Tablets (delavirdine mesylate tablets), SPORANOX (itraconazole), Stromectol (ivermectin), Taxol, Trovan, VIRACEPT (nelfinavir mesylate), Zerit (stavudine), Albenza (albendazole), Apthasol (Amlexanox), Carrington patch, Confide, Crixivan (Indinavir sulfate), Gastrocrom Oral Concentrate (cromolyn sodium), Havrix, Lamisil (terbinafine hydrochloride) Tablets, Leukine (sargramostim), Oral Cytovene, RespiGam (Respiratory Syncitial Virus Immune Globulin Intravenous), Videx (didanosine), Viramune (nevirapine), Vistide (cidofovir), Vitrasert Implant, Zithromax (azithromycin), Cedax (ceftibuten), Clarithromycin (Biaxin), Epivir (lamivudine), Intron A (Interferon alfa-2b, recombinant), Invirase (saquinavir), Valtrex (valacyclovir HCl), Western blot confirmatory device, Zerit (stavudine), and Zyrtec (cetirizine HCl).

[0377] In some embodiments, the second agent is an HDAC inhibitor.

[0378] In some embodiments, the second agent is an mTOR inhibitor, such as, *e.g.,* everolimus (RAD 001).

[0379] In some embodiments, the second agent is a proteasome inhibitor, such as, *e.g.,* bortezomib or carfilzomib.

[0380] The second agent may be an antibody or a biologic agent, such as, *e.g.,* alemtuzumab, rituximab, ofatumumab, or brentuximab vedotin (SGN-035). The second agent may be rituximab. The second agent may be rituximab and the combination therapy may be for treating, preventing, and/or managing iNHL, FL, splenic marginal zone, nodal marginal zone, extranodal marginal zone, and/or SLL.

[0381] A compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination bendamustine and one additional active agent. The cancer or hematological malignancy may be iNHL.

[0382] A compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination rituximab and one additional active agent. The cancer or hematological malignancy may be iNHL.

[0383] A compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination bendamustine and rituximab. The cancer or hematological malignancy may be iNHL.

[0384] A compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination fludarabine, cyclophosphamide, and rituximab. The cancer or hematological malignancy may be CLL.

[0385] A compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination with an antibody or a biologic agent, such as, *e.g.,* alemtuzumab, rituximab, ofatumumab, or brentuximab vedotin (SGN-035). The second agent may be rituximab. The second agent may be rituximab and the combination therapy may be for treating, preventing, and/or managing iNHL, FL, splenic marginal zone, nodal marginal zone, extranodal marginal zone, and/or SLL.

[0386] A compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof,may be used in combination with a cytotoxic agent, such as, *e.g.,* bendamustine, gemcitabine, oxaliplatin, cyclophosphamide, vincristine, vinblastine, anthracycline (*e.g.,* daunorubicin or daunomycin, doxorubicin), actinomycin, dactinomycin, bleomycin, clofarabine, nelarabine, cladribine, asparaginase, methotrexate, or pralatrexate.

[0387] A compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, may be used in combination with one or more other anti-cancer agents or chemotherapeutic agents, such as, *e.g.,* fludarabine, ibrutinib, fostamatinib, lenalidomide, thalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, or R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin or Hydroxydaunomycin, Vincristine or Oncovin, Prednisone).

[0388] Without being limited by a particular theory, it was found that a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88) does not affect BTK or MEK pathway. Accordingly, disclosed herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a BTK inhibitor. The BTK inhibitor may be ibrutinib. The BTK inhibitor may be AVL-292. The cancer or hematological malignancy may be DLBCL. The cancer or hematological malignancy may be iNHL. The cancer or hematological malignancy may be CLL.

[0389] The present disclosure also relates to a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 21, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a MEK inhibitor. The MEK inhibitor may be trametinib/GSK1120212 (*N*-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tet-

rahydropyrido[4,3-d]pyrimidin-1(2*H*)-yl}phenyl)acetamide), selumetinob (6-(4-bromo-2-chloroanilino)-7-fluoro-N-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide), pimasertib/AS703026/MSC1935369 ((S)-N-(2,3-dihydroxypropyl)-3-((2-fluoro-4-iodophenyl)amino)isonicotinamide), XL-518/GDC-0973 (1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol), refametinib/BAY869766/RDEA119 (N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide), PD-0325901 (*N*-[(2*R*)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide), TAK733 ((R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione), MEK162/ARRY438162 (5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide), RO5126766 (3-[[3-Fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-4-methyl-7-pyrimidin-2-yloxy-chromen-2-one), WX-554, RO4987655/CH4987655(3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-5-((3-oxo-1,2-oxazinan-2-yl)methyl)benzamide), or AZD8330 (2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide). The cancer or hematological malignancy may be DLBCL. The cancer or hematological malignancy may be ALL. The cancer or hematological malignancy may be CTCL.

[0390] The present disclosure also relates to a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with an EZH2 inhibitor. The EZH2 inhibitor may be EPZ-6438, GSK-126, GSK-343, EI1, or 3-deazaneplanocin A (DNNep). The cancer or hematological malignancy may be DLBCL. The cancer or hematological malignancy may be iNHL. The cancer or hematological malignancy may be ALL. The cancer or hematological malignancy may be CTCL.

[0391] The present disclosure relates to a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a bcl-2 inhibitorThe BCL2 inhibitor may be ABT-199 (4-[4-[[2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl]-N-[[3-nitro-4-[[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]sulfonyl]-2-[(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy]benzamide),ABT-737(4-[4-[[2-(4-chlorophenyl)phenyl]methyl]piperazin-1-yl]-N-[4-[[(2R)-4-(dimethylamino)-1-phenylsulfanylbutan-2-yl]amino]-3-nitrophenyl]sulfonylbenzamide), ABT-263 ((R)-4-(4-((4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholino-1-(phenylthio)btitan-2-yl)amino)-3((trifltiorometbyl)stilfonyl)phenyl)stilfonyl)benzamide), GX15-070 (obatoclax mesylate, (2Z)-2-[(5Z)-5-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-4-methoxypyrrol-2-ylidene]indole; methanesulfonic acid))), or G3139 (Oblimersen). The cancer or hematological malignancy may be DLBCL. The cancer or hematological malignancy may be iNHL. The cancer or hematological malignancy may be CLL. The cancer or hematological malignancy may be ALL. The cancer or hematological malignancy may be CTCL.

[0392] The present disclosure also relates to a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab. The patient may be an elderly patient. iNHL may be relapsed or refractory.

[0393] Also disclosed herein is a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with bendamustine. iNHL may be relapsed or refractory.

[0394] Disclosed herein is a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab, and in further combination with bendamustine. iNHL may be relapsed or refractory.

[0395] The present disclosure also relates to a method of treating or managing iNHL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with lenalidomide. iNHL may be relapsed or refractory.

[0396] Further disclosed herein is a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab. The patient may be an elderly patient. CLL may be relapsed or refractory.

[0397] Also disclosed herein is a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with bendamustine. CLL may be relapsed or refractory.

[0398] Disclosed herein is a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab, and in further combination with bendamustine. CLL may be relapsed or refractory.

[0399] The present disclosure also relates to a method of treating or managing CLL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with lenalidomide. CLL may be relapsed or refractory.

[0400] The present disclosure relates to a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein *(e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab. The patient may be an elderly patient. DLBCL may be relapsed or refractory.

[0401] Also disclosed herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with bendamustine. DLBCL may be relapsed or refractory.

[0402] Disclosed herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximab, and in further combination with bendamustine. DLBCL may be relapsed or refractory.

[0403] Also disclosed herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with R-GDP (rituximab, cyclophosphamide, vincristine and prednisone). DLBCL may be relapsed or refractory. The treatment may be done subsequent to treatment by R-CHOP.

[0404] Also disclosed herein is a method of treating or managing DLBCL comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with ibmtinib. DLBCL may be relapsed or refractory.

[0405] The present disclosure also relates to a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab. T-cell lymphoma may be relapsed or refractory.

[0406] Also disclosed herein is a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with bendamustine. T-cell lymphoma may be relapsed or refractory.

[0407] Disclosed herein is a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab, and in further combination with bendamustine. T-cell lymphoma may be relapsed or refractory.

[0408] Disclosed herein is a method of treating or managing T-cell lymphoma (PTCL or CTCL) comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with romidepsin. T-cell lymphoma may be relapsed or refractory.

[0409] Also disclosed herein is a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (e.g., salt or solvate) thereof, in combination with rituximabMantle cell lymphoma may be relapsed or refractory.

[0410] The present disclosure also relates to a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with bendamustine. Mantle cell lymphoma may be relapsed or refractory.

[0411] Also disclosed herein is a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with rituximab, an din further combination with bendamustine. Mantle cell lymphoma may be relapsed or refractory.

[0412] Additionally, disclosed herein is a method of treating or managing mantle cell lymphoma comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with ibrutinib. Mantle cell lymphoma may be relapsed or refractory.

[0413] Further, without being limited by a particular theory, it was found that cancer cells exhibit differential sensitivity profiles to doxorubicin and compounds provided herein. Thus, disclosed herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a doxorubicin. The cancer or hematological malignancy may be ALL.

[0414] Disclosed herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a AraC. The cancer or hematological malignancy may be AML

[0415] Compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88 or a pharmaceutically acceptable form thereof, may be used in combination with one or more second agent or second therapy provided herein.

[0416] The second agent may be an antibody-drug conjugate, such as, *e.g.,* inotuzumab ozogamicin, or brentuximab vedotin.

[0417] The second agent may be a cytotoxic agent, such as, *e.g.,* bendamustine, gemcitabine, oxaliplatin, cyclophosphamide, vincristine, vinblastine, anthracycline (*e.g.,* daunorubicin or daunomycin, doxorubicin), actinomycin, dactinomycin, bleomycin, clofarabine, nelarabine, cladribine, asparaginase, methotrexate, or pralatrexate.

[0418] The second agent may be one or more other anti-cancer agents or chemotherapeutic agents, such as, *e.g.,* fludarabine, ibrutinib, fostamatinib, lenalidomide, thalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, or R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin or Hydroxydaunomycin, Vincristine or Oncovin, Prednisone).

[0419] The second agent may be an antibody for a cytokine (*e.g.,* an IL-15 antibody, an IL-21 antibody, an IL-4 antibody, an IL-7 antibody, an IL-2 antibody, an IL-9 antibody). The second agent may be a JAK1 inhibitor, a JAK3 inhibitor, a pan-JAK inhibitor, a BTK inhibitor, an SYK inhibitor, or a PI3K delta inhibitor. The second agent may be an antibody for a chemokine.

[0420] Without being limited to a particular theory, a targeted combination therapy described herein has reduced side effect and/or enhanced efficacy. For example, disclosed herein is a combination therapy for treating CLL with a compound described herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88) and a second active agent (*e.g.,* IL-15 antibodies, IL-21 antibodies, IL-4 antibodies, IL-7 antibodies, IL-2 antibodies, IL-9 antibodies, JAK1 inhibitors, JAK3 inhibitors, pan-JAK inhibitors, BTK inhibitors, SYK inhibitors, and/or PI3K delta inhibitors).

[0421] Further without being limited by a particular theory, it was found that a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88) does not affect BTK or MEK pathway. Accordingly, disclosed herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a BTK inhibitor. The BTK inhibitor may be ibrutinib. The BTK inhibitor may be AVL-292. The cancer or hematological malignancy may be DLBCL. The cancer or hematological malignancy may be CLL.

[0422] The present disclosure also relates to a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a MEK inhibitor. The MEK inhibitor may be tametinib, selumetinob, AS703026/MSC1935369, XL-518/GDC-0973, BAY869766/RDEA119, GSK1120212 (trametinib), pimasertib, refametinib, PD-0325901, TAK733, MEK162/ARRY438162, RO5126766, WX-554, RO4987655/CH4987655 or AZD8330. The cancer or hematological malignancy may be DLBCL. The cancer or hematological malignancy may be ALL. The cancer or hematological malignancy may be CTCL.

[0423] Also disclosed herein is a method of treating or managing cancer or hematological malignancy comprising

administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a bcl-2 inhibitor. The BCL2 inhibitor may be ABT-199, ABT-737, ABT-263, GX15-070 (obatoclax mesylate) or G3139 (Genasense). The cancer or hematological malignancy may be DLBCL. The cancer or hematological malignancy may be ALL. The cancer or hematological malignancy may be CTCL.

[0424] Further, without being limited by a particular theory, it was found that cancer cells exhibit differential sensitivity profiles to doxorubicin and compounds provided herein. Thus, disclosed herein is a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a doxorubicin. The cancer or hematological malignancy may be ALL.

[0425] The present disclosure also relates to a method of treating or managing cancer or hematological malignancy comprising administering to a patient a therapeutically effective amount of a compound provided herein (*e.g.,* compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88), or a pharmaceutically acceptable derivative (*e.g.,* salt or solvate) thereof, in combination with a AraC. The cancer or hematological malignancy may be AML

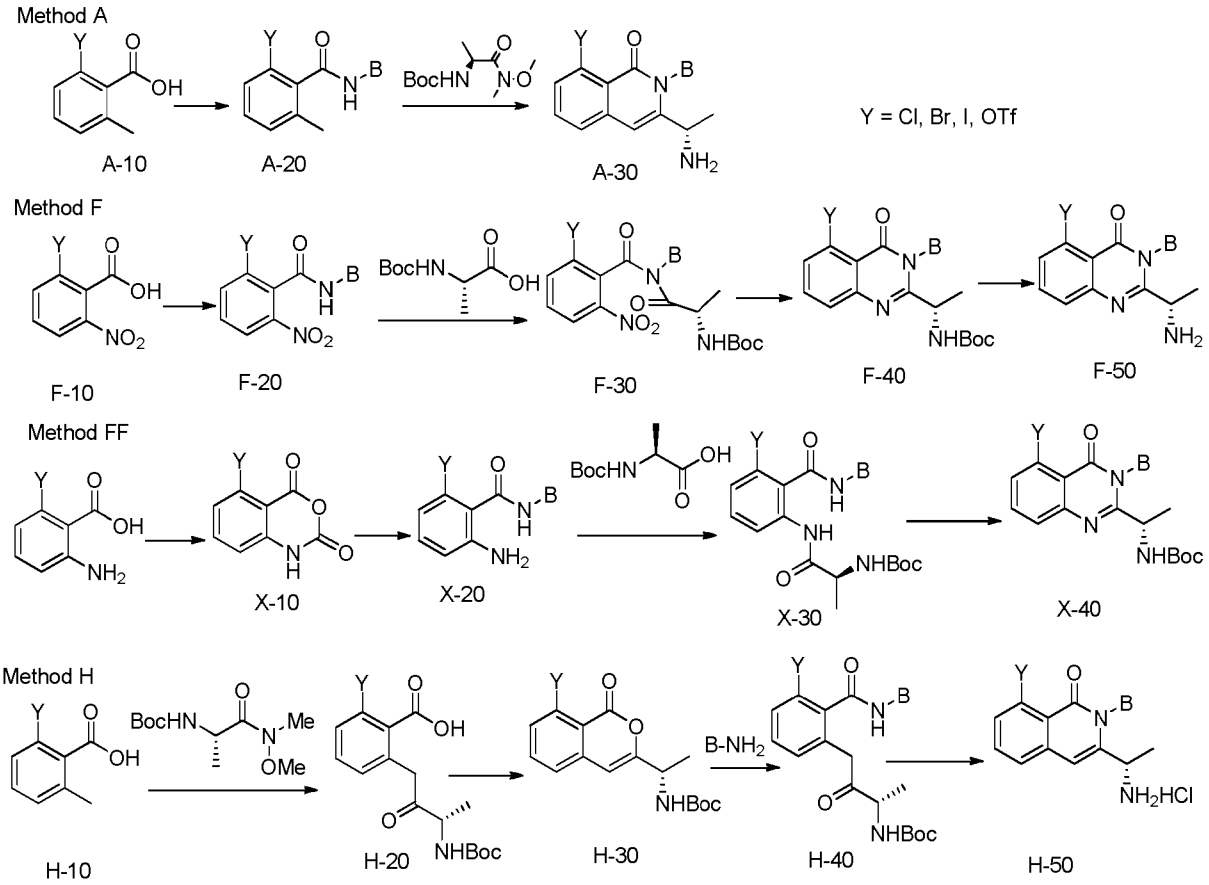
[0426] Compounds 2, 4, 7, 9, 17, 19, 26, 27, 30, 32, 35, 37, 38, 40, 41, 52, 60, 61, 63, 73, 75, 77, 79, 80, 81, and 88 or a pharmaceutically acceptable form thereof, may be used in combination with one or more second agent or second therapy provided herein.

[0427] The examples and preparations provided below further illustrate and exemplify the compounds as provided herein and methods of preparing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers can be obtained by methods known to those skilled in the art.

Synthesis of Compounds

[0428] Compounds provided herein may optionally be prepared according to methods known in the art. For example, the compounds provided herein can be synthesized according to the schemes below. Scheme 1 shows the synthesis of amine A-30 and H50. Scheme 2 shows the synthesis of amide D-20 and Formula IA.

Scheme 1

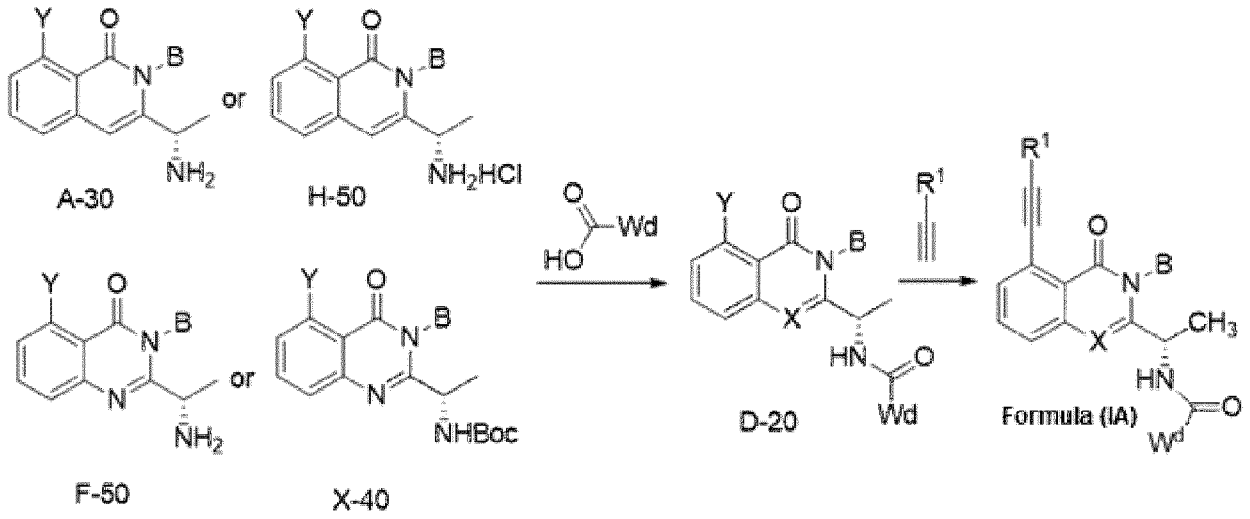


[0429] Specifically, in Scheme 1 in method A, isoquinolinone amine compound A-30 is generated in two steps. For example, in the first step, compound A-10 is converted to compound A-20. Compound A-20 is coupled with tert-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate to afford compound A-30. Isoquinolinone compounds can optionally be prepared according to method H. For example, compound H-10 is coupled with tert-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate to generate compound H-20, which is then converted to H-30. Compound H-30 is reacted with B-NH_2 to form compound H-40, which is then treated with e.g., an acid to afford H-50.

[0430] In method F, quinazolinone F-50 is generated. For example, compound F-10 is converted to compound F-20, which couples with 2-((tert-butoxycarbonyl)amino)propanoic acid to form F-30. Compound F-30 is then converted to F-40. Compound F-40 is deprotected to afford compound F-50. Alternatively, quinazolinone X-40 can be prepared starting with 2-amino-6-chlorobenzoic acid to generate compound X-10, which may be converted to compound X-20. Compound X-20 may be coupled with 2-((*tert*-Butoxycarbonyl)amino)propanoic acid to generate compound X-30, which may be converted to the desired compound X-40.

[0431] In Scheme 2, amine compound A30, F50, X-40, or H50 is treated with Wd-C(O)OH to afford amide D20, which is treated with an alkyne to generate a compound of Formula (IA).

Scheme 2



EXAMPLES

Chemical Examples

[0432] The chemical entities described herein can be synthesized according to one ormore illustrative schemes herein and/or techniques well known in the art.

[0433] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, *e.g.,* taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period that is, for example, about 1 to about 24 hours; reactions left to run overnight can average a period of about 16 hours.

[0434] The terms "solvent," "organic solvent," and "inert solvent" each mean a solvent inert under the conditions of the reaction being described in conjunction therewith including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, N-methylpyrrolidone ("NMP"), pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert organic solvents. Unless specified to the contrary, for each gram of the limiting reagent, one cc (or mL) of solvent constitutes a volume equivalent.

[0435] Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure, such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures are given by reference to the examples herein below. However, other equivalent separation or isolation procedures can also be used.

[0436] When desired, the (*R*)- and (*S*)-isomers of the non-limiting exemplary compounds, if present, can be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which can be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which can be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. Further, atropisomers (i.e., stereoisomers from hindered rotation about single bonds) of compounds provided herein can be resolved or isolated by methods known to those skilled in the art. For example, certain B substituents with ortho or meta substituted phenyl may form atropisomers, where they may be separated and isolated.

[0437] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts. Also, the compounds described herein can be optionally contacted with a pharmaceutically acceptable base to form the corresponding basic addition salts.

[0438] Optionally, compounds provided herein can generally be synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing these chemical entities are both readily apparent and

accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, e.g., from Aldrich Chemical Company (Milwaukee, WI) or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

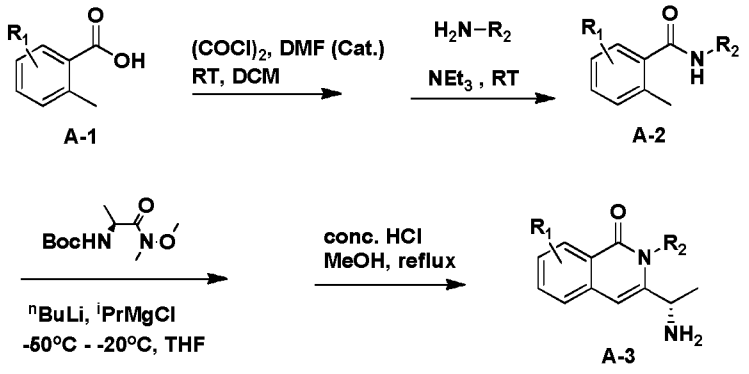
[0439] The discussion below is offered to illustrate certain of the diverse methods available for use in making the compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein.

General Synthetic Methods

[0440] The compounds herein being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments, and are not intended to limit these aspects and embodiments.

(i) General method for the synthesis of amine cores:

[0441]



Method A:

General conditions for the preparation of (*S*)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones:

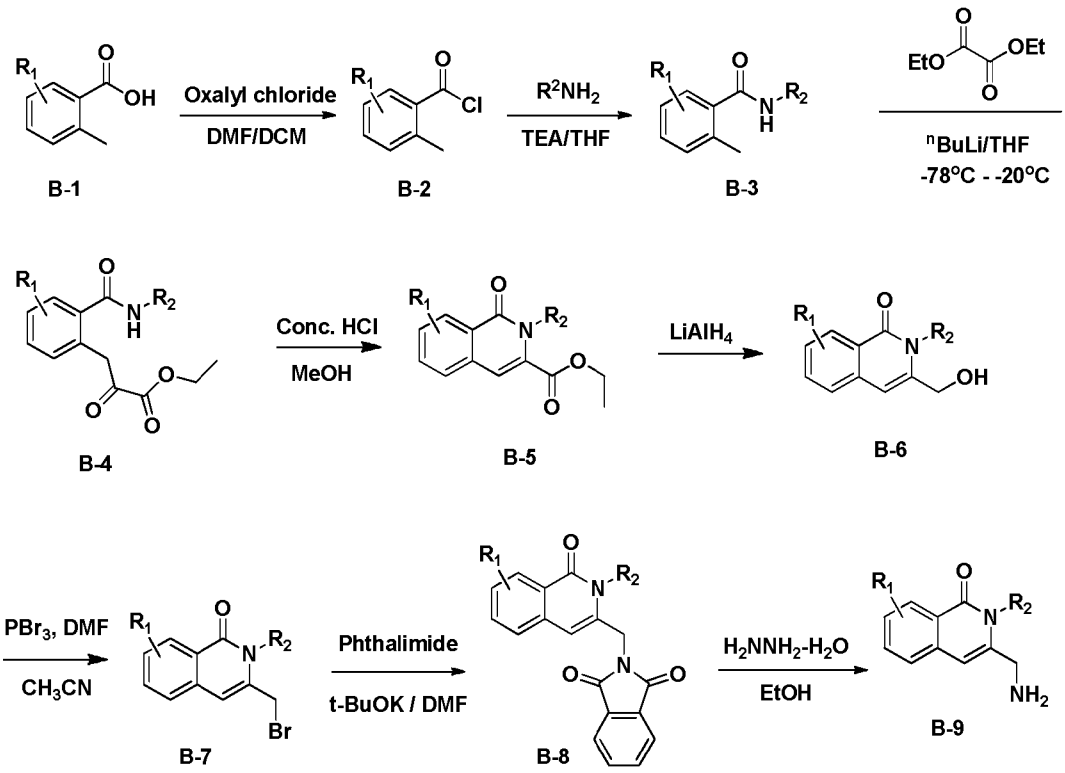
[0442] To a stirred mixture of a given *o*-methylbenzoic acid **(A-1)** (1 eq, e.g., 1.5 mol) and DMF (catalytic, e.g., 2 mL) in DCM (1.2 M, e.g., 1275 mL) at RT, oxalyl chloride (1.1 eq, e.g., 1.65 mol) is added over 5 min and the resulting mixture is stirred at RT for 2 h. The mixture is then concentrated *in vacuo*. The residue is dissolved in DCM (150 mL) and the resulting solution (solution **A)** is used directly in the next step.

[0443] To a stirred mixture of aniline (1.05 eq, e.g., 1.58 mol) and triethylamine (2.1 eq, e.g., 3.15 mol) in DCM (1.2 M, e.g., 1350 mL), the above solution **A** (e.g., 150 mL) is added dropwise while the reaction temperature is maintained between 25 °C to 40 °C by an ice-water bath. The resulting mixture is stirred at RT for 2 h and then water (e.g., 1000 mL) is added. The organic layers are separated and washed with water (2 x e.g., 1000 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The product is suspended in *n*-heptanes (e.g., 1000 mL) and stirred at RT for 30 min. The precipitate is collected by filtration, rinsed with heptanes (e.g., 500 mL) and further dried *in vacuo* to afford the amide (**A-2**).

[0444] To a stirred mixture of amide (**A-2**) (1 eq, e.g., 173 mmol) in anhydrous THF (e.g., 250 mL) at -30 °C under an argon atmosphere, a solution of *n*-butyllithium in hexanes (2.5 eq, 2.5 M, e.g., 432 mol) is added dropwise over 30 min while keeping the inner temperature between -30 °C and -10 °C. The resulting mixture is then stirred at -30 °C for 30 min.

[0445] To a stirred mixture of (*S*)-*tert*-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (1.5 eq, e.g., 260 mmol) in anhydrous THF (e.g., 250 mL) at-30 °C under an argon atmosphere, a solution of isopropylmagnesium chloride in THF (1.65 eq, 1 M, e.g., 286 mmol) is added dropwise over 30 min while keeping inner temperature between -30 °C and -10 °C. The resulting mixture is stirred at -30 °C for 30 min. This solution is then slowly added to above reaction mixture while keeping inner temperature between -30 °C and -10 °C. The resulting mixture is stirred at -15 °C for 1 h. The reaction mixture is quenched with water (e.g., 50 mL) and then acidified with conc. HCl at -10 °C to 0 °C to adjust the pH to 1-3. The mixture is allowed to warm to RT and concentrated *in vacuo*. The residue is dissolved in MeOH (*e.g.,* 480 mL), and then conc. HCl (*e.g.,* 240 mL) is added quickly at RT. The resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated *in vacuo* to reduce the volume to about 450 mL. The residue is extracted with a 2:1 mixture of heptane and ethyl acetate (e.g., 2 x 500 mL). The aqueous layer is basified with concentrated ammonium

hydroxide to adjust the pH value to 9-10 while keeping the inner temperature between -10 °C and 0 °C. The mixture is then extracted with DCM (e.g., 3 x 300 mL), washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* and the residue is dissolved in MeOH (e.g., 1200 mL) at RT. To this solution, D-(-)-tartaric acid (0.8 eq, e.g., 21 g, 140 mmol) is added in one portion at RT. After stirring at RT for 30 min, a white solid precipitates and the mixture is slurried at RT for 10 h. The solid is collected by filtration and rinsed with MeOH (e.g., 3 x 50 mL). The collected solid is suspended in water (e.g., 500 mL) and then neutralized with concentrated ammonium hydroxide solution at RT to adjust the pH to 9-10. The mixture is extracted with DCM (e.g., 3 x 200 mL). The combined organic layers are washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* to afford the (*S*)-3-(1-aniinoethyl)-isoquinolin-1(2H)-ones (**A-3**).



Method B:

General conditions for the preparation of 3-(aminomethyl)-isoquinolin-1(2H)-ones:

[0446] A mixture of benzoic acid **(B-1)** (1 eq, e.g., 400 mmol), oxalyl chloride (2 eq, e.g., 101 g, 800 mmol) and DMF (catalytic, e.g., 0.2 ml) in DCM (1M, e.g., 400 mL) is stirred at RT for 2 h. The mixture is concentrated *in vacuo* to afford the acid chloride (**B-2**). The product obtained is used directly in the next step without further purification.

[0447] A mixture of R_2NH_2 amine (1.05 eq, e.g., 420 mmol) and triethylamine (1.7, e.g., 700 mmol) in DCM (1.4 M, e.g., 300 mL) is stirred at RT for 10 min. To this mixture, acid chloride (**B-2**) (1 eq, e.g., 400 mmol) is added dropwise, and the resulting mixture is stirred at RT for 30 min. The reaction mixture is poured into water (e.g., 300 mL) and extracted with DCM (e.g., 3 x 200 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product. The product is suspended in isopropyl ether (e.g., 300 mL), stirred at reflux for 30 min, and then cooled to 0-5 °C. The precipitate is collected by filtration and further dried *in vacuo* to afford the product amide (**B-3**).

[0448] To a stirred solution of amide (**B-3**) (1.0 eq, e.g., 0.1 mol) in anhydrous THF (0.4 M, e.g., 225 mL) at -78 °C under an argon atmosphere, a solution of *n*-butyllithium in hexanes (2.5 M, 3 eq, e.g., 120 mL, 0.3 mol) is added dropwise over 1 h period of time while keeping inner temperature between -78 °C to -50 °C. The resulting mixture is stirred at -70°C for 1 h, and then diethyl oxalate (1.2 eq, e.g., 17.5 g, 0.12 mol) is quickly added (with an increase in temperature to -20 °C upon addition). The mixture is stirred at -50 °C for 10 min, and then quenched with water (e.g., 100 mL). The inorganic salt is removed by filtration, and the filtrate is washed with ethyl acetate (e.g., 2 x 100 mL). The combined organic layers are washed with brine (e.g., 100 mL), dried over $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* to afford the product as a semi-solid. The product is slurried in isopropyl ether (e.g., 100 mL) at RT for 10 min. The solid is collected by filtration and further dried *in vacuo* to afford the product (**B-4**). The product obtained is used directly in

the next step.

[0449] Compound (**B-4**) (1 eq, e.g., 88 mmol) is dissolved at 0.9 M with HCl/MeOH (100 mL, e.g., 10 M), and the resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated *in vacuo,* and the residue is slurried in ethyl acetate (100 mL) at RT for 30 min. The solid is collected by filtration, rinsed with ethyl acetate (3 x 50 mL), and further dried *in vacuo* to afford the product (**B-5**).

[0450] To a stirred suspension of lithium aluminum hydride (3 eq., e.g., 15.6 g, 410 mmol) in anhydrous THF (0.3 M, e.g., 500 mL) at -78 °C under a nitrogen atmosphere, (**B-5**) (1 eq, e.g., 137 mmol) is slowly added over a 10 min period of time. The resulting mixture is allowed to warm to -30 °C and stirred for 30 min. The mixture is then cooled to -78 °C, and quenched carefully with water (e.g., 100 mL). The mixture is allowed to warm to RT, filtered through silica gel (e.g., 20 g), and the filtrate is concentrated *in vacuo*. The product mixture is poured into H_2O (e.g., 200 mL) and extracted with ethyl acetate (e.g., 3 x 200 mL). The combined organic layers are washed with brine (e.g., 100 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The product is suspended in ethyl acetate (e.g., 30 mL) and stirred for 10 min. The solid is collected by filtration and further dried *in vacuo* to afford the product (**B-6**).

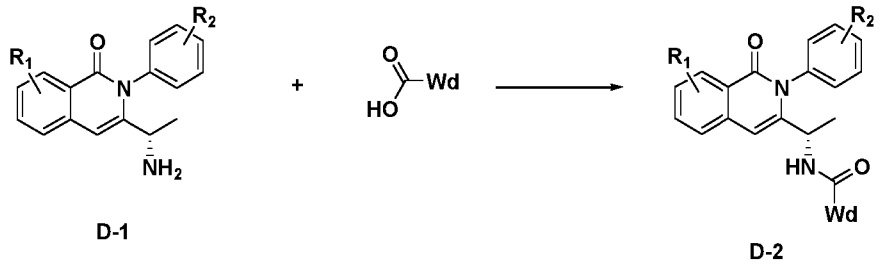
[0451] Phosphorus tribromide (1.2 eq, e.g., 3.42 g, 12.6 mmol) and DMF (2.0 eq, e.g., 1.6 g, 21.0 mmol) is dissolved in CH_3CN (0.13 M, e.g., 100 mL) and the resulting mixture is stirred at -10 °C for 10 min. To this mixture, alcohol (**B-6**) (1.0 eq, 10.5 mmol) is added in portions. The resulting mixture is allowed to warm to RT and stirred for an additional 30 min. The reaction mixture is neutralized with saturated aqueous $NaHCO_3$ solution at 0-5 °C and then filtered. The filtrate is extracted with ethyl acetate (e.g., 3 x 100 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (20 % ethyl acetate-petroleum ether) to afford the product bromide (**B-7**).

[0452] To a stirred mixture of phthalimide (1.1 eq, e.g., 6.93 mmol) in DMF (e.g., 20 mL) at RT, potassium-*tert*-butoxide (1.5 eq, e.g., 1.1 g, 9.45 mmol) is added in portions over 10 min and then bromide (**B-7**) (1.0 eq, e.g., 6.3 mmol) is added. The resulting mixture is stirred at 100 °C for 2 h. The reaction mixture is allowed to cool to RT and then poured into ice-water (e.g., 30 mL). The mixture is extracted with ethyl acetate (e.g., 3 x 20 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (e.g., 16% ethyl acetate-petroleum ether) to afford the product dione (**B-8**).

[0453] Dione (**B-8**) (1.0 eq, e.g., 1.5 mmol) and hydrazine hydrate (e.g., 8.0 eq, 600 mg, 12 mmol) are dissolved in EtOH (e.g., 20 mL) and the resulting mixture is stirred at reflux for 1 h. The mixture is allowed to cool to RT and then filtered. The filter cake is washed with EtOH (e.g., 10 mL). The combined filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (e.g., 2.5% MeOH-DCM) to afford the amine (**B-9**).

(ii) General methods for amide synthesis:

[0454]



D-1 D-2

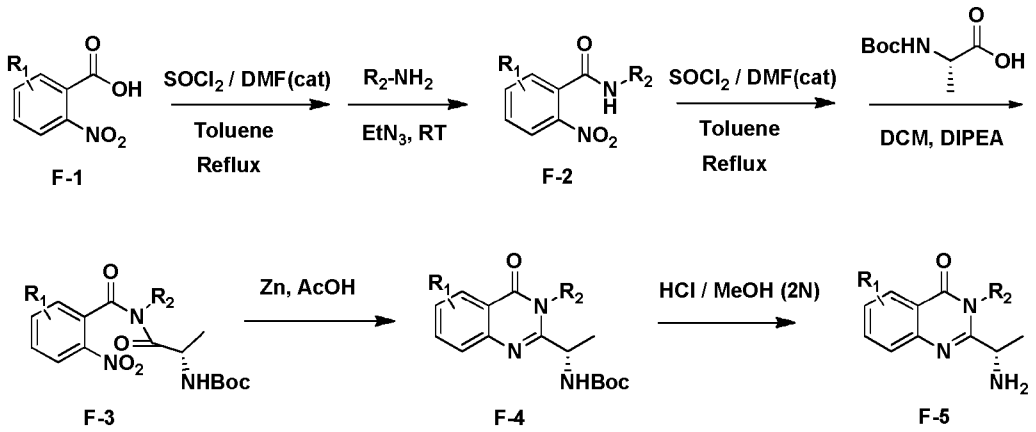
Method D:

[0455] To a mixture of amine **(D-1)** (1.0 eq, e.g., 0.5 mmol), W_d-COOH carboxylic acid (1.1 eq, e.g., 0.55 mmol), and *N,N*-diisopropylethylamine (2.0 eq, e.g., 0.17 mL, 1.0 mmol) in anhydrous DMF (e.g., 5 mL), 1-hydroxybenzotriazole hydrate (1.3 eq, e.g., 0.65 mmol) and EDC hydrochloride (1.3 eq, e.g., 0.65 mmol,) are added sequentially and the resulting mixture is stirred at RT for 2-16 h. Ice-water or saturated sodium carbonate solution is added to the reaction mixture and then stirred for 10 min. The precipitate is collected by filtration, rinsed with water and dried *in vacuo*. The solid collected is further purified by flash column chromatography on silica gel (e.g., 0-10% MeOH-DCM) to afford the product amide (**D-2**).

Method E:

[0456] A solution of amine **(D-1)** (1 eq, e.g., 0.25 mmol), W_d-COOH carboxylic acid (1.1 eq), and 1-hydroxybenzotriazole

hydrate (1.3 eq) in dimethylformamide (0.1 M) is treated with diisopropylethylamine (2 eq) and then EDC hydrochloride (1.3 eq, e.g., 63 mg). The reaction mixture is stirred at ambient temperature overnight. The reaction mixture is diluted with water (5x solvent) and acetic acid (1.5 eq) is added, then the mixture is stirred in an ice bath for 40 min. The resulting precipitate is collected by filtration, and washed with water (e.g., 3x 3 mL). The collected solid is dried *in vacuo* to afford amide (**D-2**).



Method F:

[0457] To a stirred mixture of nitrobenzoic acid **(F-1)** (1.0 eq, 1.0 mol) and DMF (e.g., 2.0 mL) in toluene (e.g., 800 mL), thionyl chloride (4.0 eq, e.g., 292 mL, 1.0 mol) is added dropwise (over 15 min) and the resulting mixture is stirred at reflux for 1.5 h. The mixture is allowed to cool to RT and then concentrated *in vacuo*. The residue is dissolved in DCM (e.g., 100 mL) to form solution A, which is used directly in the next step.

[0458] To a stirred mixture of a given amine R_2-NH_2 (1.1 eq, e.g., 102.4 g, 1.1 mol) and triethylamine (2.0 eq, e.g., 280 mL, 2.0 mol) in DCM (1.6 M, e.g., 700 mL), solution A is added dropwise while keeping the reaction temperature below 10 °C. The resulting mixture is allowed to warm to RT and then stirred at RT overnight. The reaction mixture is diluted with ice-water (e.g., 1.0 L) and stirred for 15 min. The precipitate is collected by filtration, rinsed with isopropyl ether (e.g., 3 x 100 mL) and petroleum ether (e.g., 3 x 100 mL), and then dried *in vacuo* to afford product amide (**F-2**).

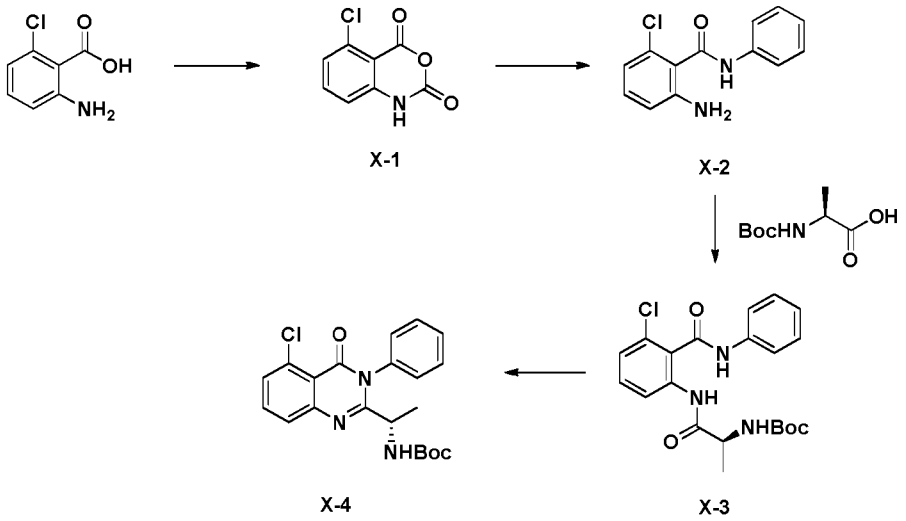
[0459] A mixture of nitro-benzamide (**F-2**) (1.0 eq, e.g., 20.0 mmol,) and DMF (cat.) in toluene (0.3 M, e.g., 60 mL) at RT, thionyl chloride (8.2 eq, e.g., 12 mL , 164 mmol) is added dropwise (over 5 min) and the resulting mixture is stirred at reflux for 2 h. The mixture is allowed to cool to RT and then concentrated *in vacuo*. The residue is dissolved in DCM (e.g., 10 mL) to form solution B, which is used directly in the next step.

[0460] To a stirred mixture of *N*-(*tert*-butoxycarbonyl)-L-alanine (0.8 eq, e.g., 16.0 mmol) and *N,N*-diisopropylethylamine (1.5 eq, e.g., 4.0 g, 31.0 mol) in DCM (0.8 M, e.g., 20 mL), solution B is added dropwise while keeping the reaction temperature between 0-10 °C. The resulting mixture is stirred at this temperature for 1 h and then stirred at RT overnight. The reaction mixture is quenched with ice-water (e.g., 100 mL). The organic layer is separated and the aqueous layer is extracted with DCM (e.g., 2 x 80 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is slurried in isopropyl ether (e.g., 100 mL) for 15 min. The solid is collected by filtration and dried *in vacuo* to afford product (**F-3**).

[0461] To a suspension of zinc dust (10.0 eq, e.g., 7.2 g, 110 mmol) in glacial acetic acid (2.8 M, *e.g.,* 40 mL) at 15 °C, a solution of (**F-3**) (1.0 eq, e.g., 11.0 mmol) in glacial acetic acid (0.3 M, e.g., 40 mL) is added and the resulting mixture is stirred at RT for 4 h. The mixture is poured into ice-water (e.g., 200 mL) and neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 8. The resulting mixture is extracted with DCM (e.g., 3 x 150 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash chromatography on silica gel (7% ethyl acetate-petroleum ether) to afford product (**F-4**).

[0462] Compound (**F-4**) (1.0 eq, e.g., 0.5 mmol) is dissolved in hydrochloric methanol solution (8 eq, e.g., 2N, 20 mL) and the resulting mixture is stirred at RT for 2 h. The mixture is concentrated *in vacuo*. The residue is diluted with water (30 mL) and then neutralized with saturated aqueous $NaHCO_3$ to adjust the pH to 8 while keeping the temperature below 5 °C. The resulting mixture is extracted with DCM (e.g., 3 × 30 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is slurried in petroleum ether (e.g., 10 mL). The solid is collected by filtration and dried *in vacuo* to afford product (**F-5**).

[0463] The quinazolinone (**F-5**) can be used to synthesize comparative compounds described herein using, for example, Method D to couple the amine to W_d groups.



Method FF

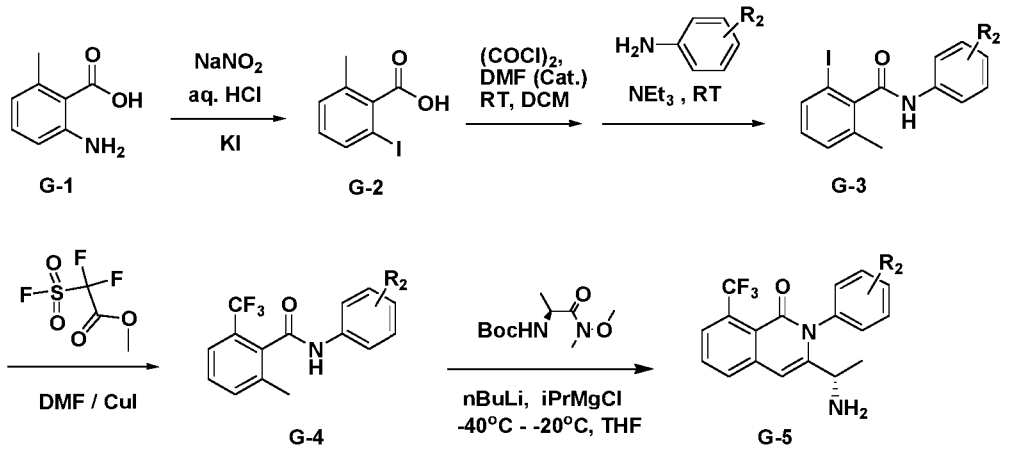
[0464] Alternatively, compounds with a quinazolinone core can be prepared according to the procedures in PCT publication no. WO2013082540.

[0465] In Method FF, 2-Amino-6-chlorobenzoic acid (63 mmol, 1.0 equiv) is dissolved in acetonitrile (60 mL) in a 250 mL round bottomed-flask, placed under an atmosphere of Ar and heated to 50 °C. Pyridine (2.0 equiv) is added followed by dropwise the addition of a solution of triphosgene (0.34 equiv in 30 mL acetonitrile) while maintaining the internal temperature below 60 °C. The mixture is then stirred at 50 °C for 2h after which the solvent is removed under vacuum. The remaining residue is dispersed in 50 mL of water and filtered. The resulting solid is washed with a minimal amount of acetonitrile to remove discoloration and then dried to provide desired anhydride **X-1.**

[0466] Anhydride **X-1** (25.5 mmol, 1.0 equiv) is suspended in dioxane (40 mL) under an atmosphere of Ar in a 200 mL round bottomed- flask. Aniline (1.0 equiv) is added dropwise. Heating is started at 40 °C and gradually increased to 100 °C. After 4h, the majority of starting material is consumed after which the reaction is allowed to cool. The solvent is then removed under vacuum to provide an oil which is redissolved in toluene followed by the addition of hexanes until the solvent appears close to partionning. The mixture is stirred for 14h after which a solid appeared in the flask. This solid is isolated via vacuum filtration and washed with hexanes to provide the desired amide **X-2** in high yield.

[0467] (*S*)-2-((*tert*-Butoxycarbonyl)amino)propanoic acid (33.0 mmol, 2.0 equiv) is dissolved in dry tetrahydrofuran (70 mL) under an atmosphere of Ar after which *N*-methylmorpholine (2.2 equiv) is added dropwise. The mixture is then cooled to -17 °C in an acetone/dry ice bath after which a solution of isobutyl chloroformate (2.0 equiv in 10 mL of dry tetrahydrofuran) is added dropwise to the mixture followed by stirring for 30 min. A solution of amine **X-2** (10 equiv in 10 mL of dry tetrahydrofuran) is then added. The dry ice bath is then removed and the mixture is stirred at RT for 90 min. It is then heated to 60 °C for another 2h after which it is allowed to cool. MTBE (150 mL) and water (150 mL) are then successively added with strong stirring. The phases are separated and the organic phase is washed with water (2 x 50 mL) and brine (50 mL) and dried over sodium sulfate. The solution is then concentrated under reduced pressure and the crude reside is purified using flash silica gel chromatography (gradient 5-30 ethyl acetate/hexanes) **X-3** as the coupled product.

[0468] Compound **X-3** (4.9 mmol, 1.0 equiv) is then suspended in acetonitrile (100 mL). Triethylamine (48 equiv) is then added with stirring followed by the dropwise addition of chlorotrimethylsilane (15 equiv). The flask is then sealed and heated to 90 °C for 3d. The reaction is allowed to cool after which the solvent is removed under vacuum. The residue is then dissolved in ethyl acetate (120 mL) and successively washed with saturated sodium carbonate (1 x 100 mL), water (1 x 100 mL) and brine (1 x 100 mL). The organic layer is then dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide cyclized product **X-4.** The product can either be used directly in subsequent reactions or purified using flash silica gel chromatography.



Method G:

General conditions for the preparation of (*S*)-3-(1-aminoethyl)1-8-(trifluoromethyl)isoquinolin-1(2H)-ones:

[0469] To a suspension of 2-amino-6-methylbenzoic acid (**G-1**) (20.0 g, 132.0 mmol, 1.0 eq) in H_2O (55 mL) at 0-5 °C, conc. HCl (36.5 %, 64 mL, 749 mmol, 5.7 eq) is added slowly. After stirring for 15 min, the mixture is added dropwise to a solution of sodium nitrite (12.02 g, 174.0 mmol, 1.32 eq) in H_2O (36 mL) at 0-5 °C, and the resulting mixture is stirred for 1 h. The resulting solution is then added to a solution of KI (60.5 g, 364.5 mmol, 2.76 eq) in H_2O (150 mL) at 0-5 °C. The reaction mixture is allowed to warm to RT and stirred at RT overnight. The mixture is extracted with ethyl acetate (3 x 100 mL). The combined organic layers are washed with water (2 x 100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (0-20% ethyl acetate-petro ether) to afford the product, 2-iodo-6-methylbenzoic acid (**G-2**).

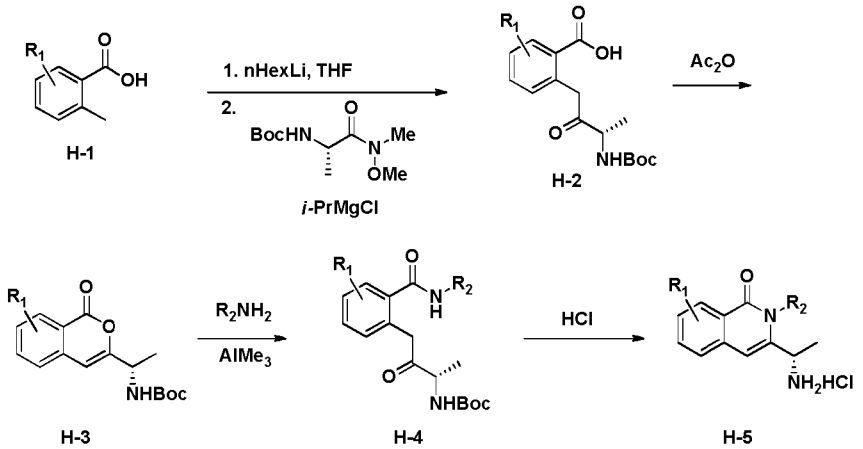
[0470] To a stirred mixture of 2-iodo-6-methylbenzoic acid (**G-2**) (305.3 mmol, 1.0 eq) and DMF (0.3 mL) in DCM (350 mL) at RT, oxalyl chloride (466.4 mmol, 1.5 eq) is added dropwise. The resulting mixture is stirred at RT for 3 h and then concentrated *in vacuo*. The residue is dissolved in DCM (50 mL) and the resulting solution (solution A) is used directly in the next step.

[0471] To a stirred mixture of R_3-substituted aniline (335.7 mmol, 1.1 eq) and triethylamine (915.0 mmol, 3.0 eq) in DCM (350 mL), solution A (150 mL) is added dropwise while the reaction temperature is controlled below 30 °C by an ice-water bath. The reaction mixture is stirred at RT for 1 h and then quenched with water (200 mL). The organic layer is separated, washed with water (2 x 200 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The product is rinsed with isopropyl ether and dried *in vacuo* to afford the product amide (**G-3**).

[0472] A mixture of amide (**G-3**) (18.0 mmol, 1.0 eq), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (72.9 mmol, 4.0 eq) and CuI (3.63 mmol, 0.2 eq) in DMF (130 mL) is stirred at 70 °C under an argon atmosphere overnight. The mixture is allowed to cool to RT and then concentrated *in vacuo* to remove the solvent. The resulting residue is partitioned between ethyl acetate (60 mL) and water (60 mL), and the aqueous layer is extracted with ethyl acetate (2 x 60 mL). The combined organic layers are washed with water (2 x 60 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel to afford the product, trifluoromethyl amide (**G-4**).

[0473] To a stirred mixture of amide (**G-4**) (10.1 mmol, 1.0 eq) in anhydrous THF (25 mL) at -40 °C under an argon atmosphere, a solution of *n*-butyllithium in THF (2.5 M, 25.3 mmol, 2.5 eq) is added dropwise (over 15 min) and the inner temperature is controlled between -30 °C and -20 °C during the addition. The resulting mixture is stirred at -30 °C for an additional 1 h. To a stirred mixture of (*S*)-*tert*-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (11.1 mmol, 1.1 eq) in anhydrous THF (20 mL) at-30 °C under an argon atmosphere, a solution of isopropylmagnesium chloride in THF (12.6 mmol, 1.25 eq) is added dropwise (over 15 min) and the inner temperature is controlled below -20 °C during the addition. The resulting mixture is stirred at -15 °C for 1 h. This solution is then slowly added to above reaction mixture at -30 °C (over 10 min), and the resulting mixture is stirred at -30 °C for an additional 30 min. The reaction mixture is quenched with water (50 mL) and then acidified with conc. HCl at -5 °C to adjust the pH to 5. The mixture is allowed to warm to RT and concentrated *in vacuo*. The residue is dissolved in MeOH (10 mL), and then conc. HCl (10 mL) is added quickly at RT. The resulting mixture is stirred at reflux for 2 h, cooled to RT and then concentrated *in vacuo*. The residue is suspended in water (15 mL), basified with concentrated ammonium hydroxide to adjust the pH to 9-10 while keeping the inner temperature below 5 °C and then extracted with DCM (3 x 15 mL). The combined organic layers are washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* and the residue is dissolved in MeOH

(70 mL). To this solution, D-(-)- tartaric acid (8.1 mmol, 0.8 eq) is added in one portion at RT. After stirring at RT for 30 min, a solid precipitates and the mixture is slurried at RT for 10 h. The precipitate is collected by filtration and rinsed with MeOH (3 x 4.0 mL). The collected solid is suspended in water (30 mL) and then neutralized with concentrated ammonium hydroxide solution at RT to adjust the pH to 9-10. The mixture is extracted with DCM (3 x 15 mL). The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* to afford the product, (*S*)-3-(1-aminoethyl)-8-(trifluoromethyl)isoquinolin-1(2H)-one (**G-5**).



Method H:

General conditions for the preparation of (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones:

[0474] An o-methylbenzoic acid (**H-1**) (1 eq, e.g., 46.9 mmol) in a flame-dried round bottom flask under nitrogen is dissolved in THF (1 M, e.g., 50 mL). The resulting homogeneous yellow solution is cooled to -25 °C and n-hexyllithium (4.3 eq, e.g., 202 mmol;2.3 M in hexanes) is slowly added, after which the solution becomes dark red and is stirred at -20 °C for 20 min.

[0475] (S)-Tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (1.3 eq, e.g., 61.0 mmol) is charged into a second dry round bottom flask under N_2 and suspended in 70 mL of dry THF and cooled to -10 °C. Isopropyl magnesium chloride (2 M, 2.7 eq, e.g., 127 mmol) is slowly added resulting in a clear yellow solution. This solution is then slowly canulated dropwise into the first round bottom flask. After addition is complete, the dark solution is slowly warmed to RT and stirred at RT for 2 h. The reaction mixture is then recooled to -10 °C and quickly canulated into another flask fitted with ethyl acetate (e.g., 15 mL) and isobutyric acid (e.g., 10 mL) at -10°C under N_2. During this time the mixture goes from orange and cloudy to clear and homogeneous. After addition, the mixture is stirred for 5 min after which water (e.g., 10 mL) is rapidly added and it is stirred vigorously for 10 min at RT.

[0476] The mixture is then transferred to a separation funnel, and water (e.g., 200 mL) is added to dissolve salts (pH ~ 9). The water layer is extracted with EtOAc (e.g., 3 x 400 mL). The aqueous layer is then acidified with HCl (2 M) to pH 3, and then extracted with EtOAc (e.g., 3 x 500 mL), dried over sodium sulfate and concentrated to provide crude material which is filtered under vacuum through a pad of silica gel using a MeOH/DCM (gradient of 2-10% MeOH) to provide the acid **H-2** after concentration.

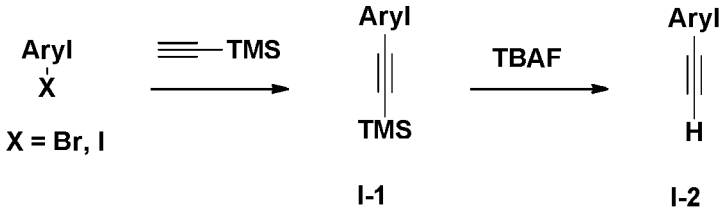
[0477] A 50 mL round bottom flask with a stir bar is filled with benzoic acid **H-2** (1 eq., e.g., 14.63 mmol) in acetic anhydride (1.5 M, e.g., 10 mL) and then stirred at 70 °C for 2.5 hours until complete conversion to the product is indicated by LC/MS. The acetic anhydride is evaporated under reduced pressure and the crude residue is purified with combiflash (gradient of EtOAc/hexanes) to give the lactone **H-3.**

[0478] A 50 mL dry round bottom flask with a stir bar is filled with amine R_2NH_2 (5.1 eq, e.g., 1.54 mmol) in 2 mL of DCM (0.8 M) after which trimethylaluminum (5.1 eq, e.g., 1.54 mmol) is added to the solution and stirred for 15 min. A solution of lactone **H-3** (1.0 eq, e.g., 0.31 mmol) in DCM (1.5 M, e.g., 2 mL) is then added. The mixture is then stirred at RT for 3 h until LC/MS analysis showed complete formation of the desired product. The reaction mixture is quenched with 10 mL of Rochelle's salt and stirred for 2 h. The mixture is then diluted with DCM, washed with brine, dried with over sodium sulfate and evaporated to give a yellow sticky liquid **H-4** which is used directly in next step.

[0479] To the amide **H-4** (1 eq, e.g., 0.31 mmol) in isopropanol (0.06 M, e.g., 5 mL) was added 3 mL of concentrated HCl (300 eq). The mixture is then heated in an oil bath at 65 °C for 3 h until LC/MS shows no remaining starting material. The flask is then removed from heat and the solvents are evaporated under reduced pressure to provide a yellow solid **H-5** which is used directly in subsequent transformations.

(iii) General methods for alkyne synthesis:

[0480]



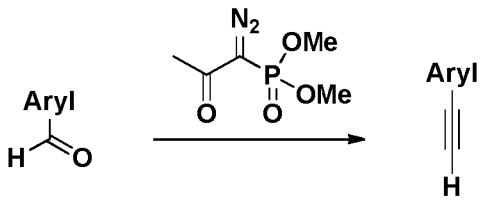
Method I

[0481] A sealed vessled is chared with $PdCl_2(MeCN)_2$ and X-Phos (3:1 ratio of X-Phos to $PdCl_2(MeCN)_2$, 5-15 mol% catalyst), cesium carbonate (1.5-3.0 equiv) and propionitrile (0.5 M). The mixture is stirred for 5 min after which the aryl bromide or aryl iodide substrate was added. After another 5 minutes of stirring TMS-acetylene (3.0 equiv) is added and the flask is sealed and heated at RT for 10 min follwed by 1h of heating at 95 °C. The reaction is allowed to cool after which it is concentrated directly onto silica gel and purified using flash silica gel chromatography (gradient of ethyl acetate/hexanes) to provide alkyne **I-1.**

[0482] Alkyne **I-1** (1.0 equiv) is then dissolved in tetrahydrofuran (0.13 M) and charged with TBAF (1.1 equiv, 1.0 M in tetrahydrofuran). The resulting mixture is stirred at RT for 6h after which it is poured into saturated bicarbonate solution and extracted with ethyl acetate. The organic layer is washed with brine and concentrated onto silica gel where it is purifed directly by flash silica gel chromatography (gradient of ethyl acetate/hexanes) to provide aryl alkyne **I-2.**

Method J

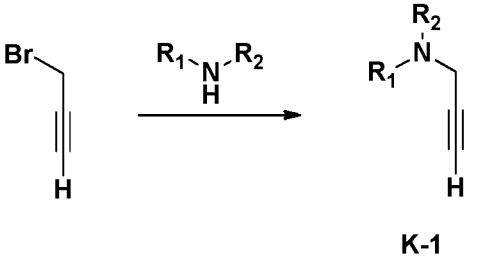
[0483]



[0484] Aldehyde (1.0 equiv) was a dissolved in anhydrous methanol (0.2-0.5 mM) and charged with cesium carbonate (1.0 equiv) and cooled to 0-5 °C . Dimethyl (1-diazo-2-oxopropyl)phosphonate (1.0 equiv) was added dropwise after which the reaction was allowed to stir for 1-18h after which the crude mixture was concentrated onto silica gel and purified directly by flash silica gel chromatography to provide the desired alkyne **J-1.**

Method K

[0485]

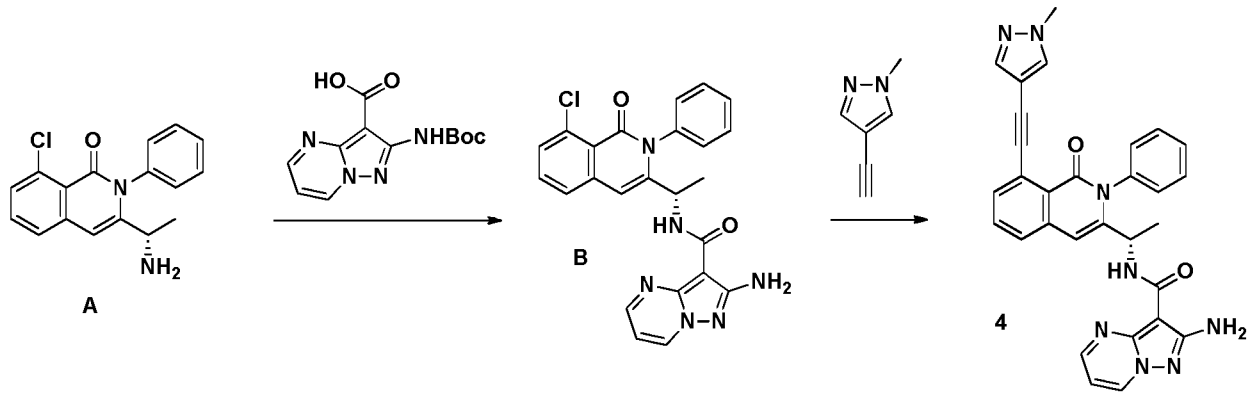


[0486] A secondary amine (1.0 equiv) is dissolved in acetonitrile (0.42 M) and potassium carbonate (1.1 equiv) was

added. The white suspension was stirred at 0-5 °C for 5 min after which point propargyl bromide (1.01 equiv) was added dropwise over 3 min. The reaction was then stirred for an additional 15 min at 0-5 °C and then at room temperature for 15h. The heterogeneous mixture was then filtered. The filtrate was concentrated under reduced pressure, dilluted with MTBE and washed with water (2x), brine (1x), dried over sodium sulfate and then filtered through celite. The resulting filtrate was concentrated and purified using flash silica gel chromatography to provide the desired alkyne **K-1.**

Example 1

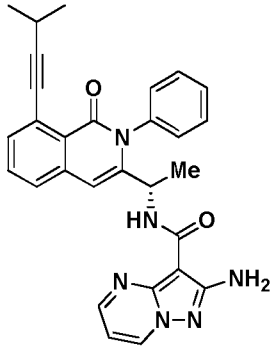
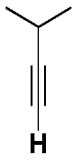
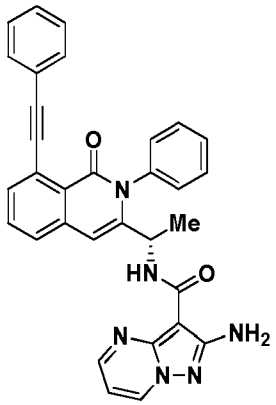
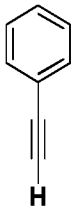
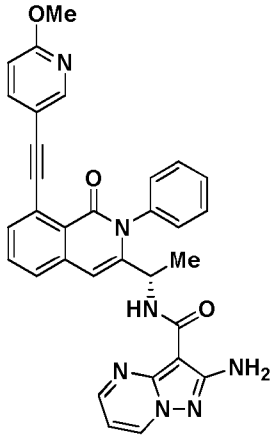
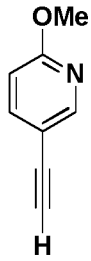
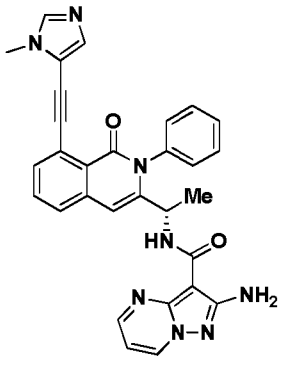
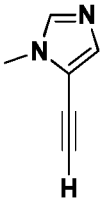
[0487]



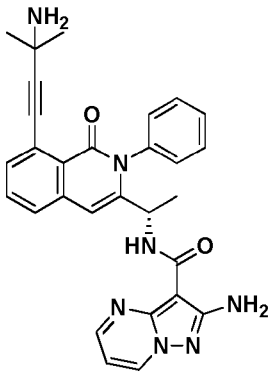
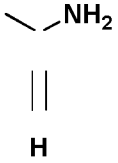
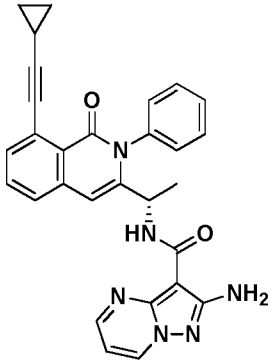
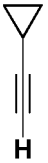
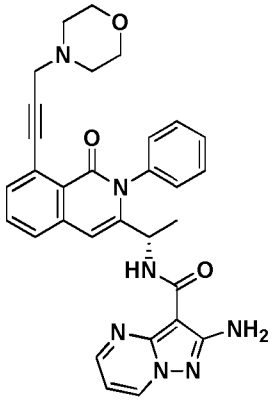
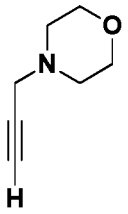
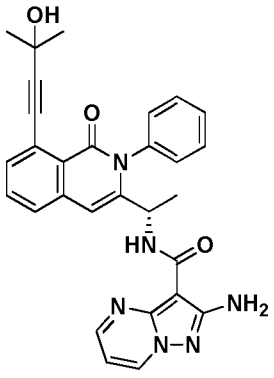
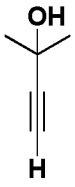
[0488] Compound 4 was prepared in 3 steps from compound A according to the following procedures: Compound A was prepared according to Method A. It was coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid according to the following procedure: Compound A (27.4 mmol, 1.0 equiv), HOBt hydrate (1.2 equiv), 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (1.05 equiv) and EDC (1.25 equiv) were added to a 200 mL round bottomed flask with a stir bar. N,N-Dimethylformamide (50 mL) was added and the suspension was stirred at RT for 2 min. Hunig's base (4.0 equiv) was added and after which the suspension became homogeneous and was stirred for 22h resulting in the formation of a solid cake in the reaction flask. The solid mixture was added to water (600 mL) and stirred for 3h. The resulting cream colored solid was filtered and washed with water (2 x 100 mL) and dried. The solid was then dissolved in methylene chloride (40 mL) after which trifluoroacetic acid (10 equiv, 20 mL) was added and the reaction was stirred for 30 min at RT after which there is no more starting material by LC/MS analysis. The solution was then concentrated and coevaporated with a mixture of methylene choride/ethanol (1:1 v/v) and then dried under high vacuum overnight. The resulting solid was triturated with 60 mL of ethanol for 1h and then collected via vacuum filtration. The beige solid was then neutralized with sodium carbonate solution (100 mL) and then transferred to a separatory funnel with methylene chloride (350 mL). The water layer was extracted with an additional 100 mL of methylene chloride. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum to provide a pale yellow solid that was purified using flash silica gel chromatography (Combiflash, 24g column, gradient of 0-5% methanol/methylene chloride) to provide amide **B.** ESI-MS m/z: 459.4 [M+H]+.

[0489] Amide B was placed in a sealed tube (0.67 mmol, 1.0 equiv) followed by dichlorobis(acetonitrile)palladium (15 mol%), X-Phos (45 mol%), and cesium carbonate (3.0 equiv) Propionitrile (5 mL) was added and the mixture was bubbled with Ar for 1 min. 4-Ethynyl-1-methyl-1H-pyrazole (1.24 equiv) was added and the resulting orange mixture was sealed and stirred in an oil bath at 85 oC for 1.5h. The resulting brownish-black mixture was allowed to cool at which point there was no more SM by LC/MS analysis. The mixture was then filtered through a short plug of cotton using acetonitrile and methylene chloride. The combined filtrates were concentrated onto silica gel and purified using flash silica gel chromatography (Combiflash, 4g column, gradient of 0-5% methylene chloride/methanol). The resulting material was further purified by reverse phase HPLC (15-90% acetonitrile with 0.1% formic acid/water with 0.1% formic water) to provide desired compound 4. ESI-MS m/z: 529.5 [M+H]+.

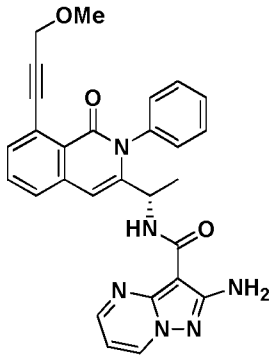
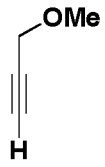
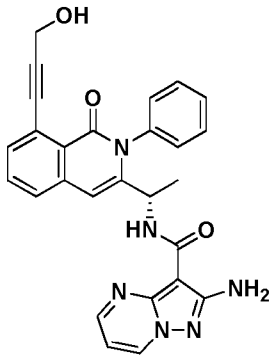
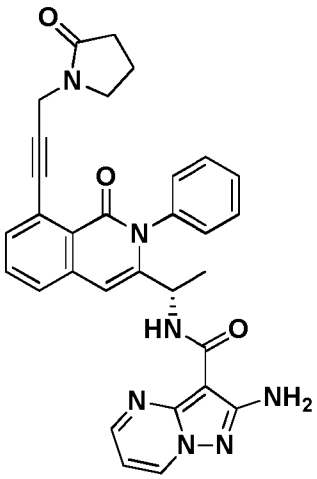
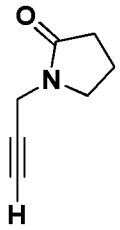
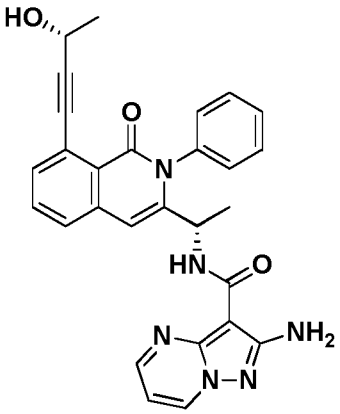
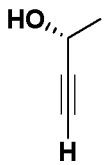
[0490] The following compounds were prepared in analogous fashion. The alkynes were either commercially available or prepared using Method I, J, or K as described herein.

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 2			491.1 $[M+H]^+$
Compound 5			525.5 $[M+H]^+$
Compound 6			556.3 $[M+H]^+$
Compound 7			529.5 $[M+H]^+$

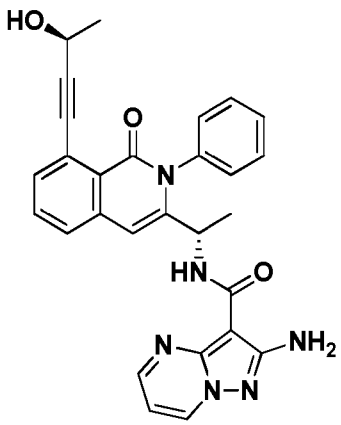
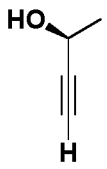
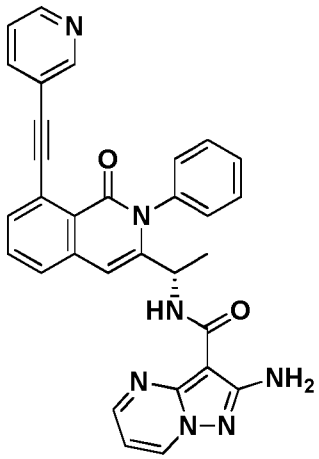
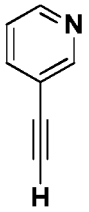
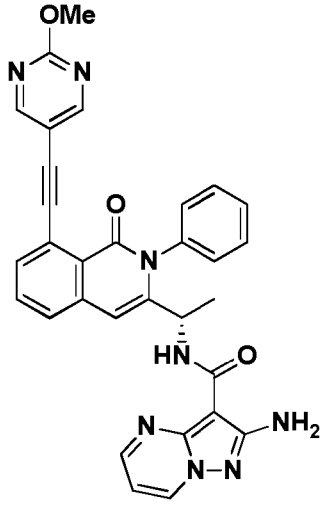
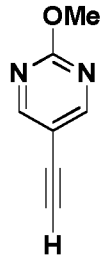
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 8			506.1 $[M+H]^+$
Compound 9			489.4 $[M+H]^+$
Compound 10		 Synthesized according to Method K	548.6 $[M+H]^+$
Compound 11			507.1 $[M+H]^+$

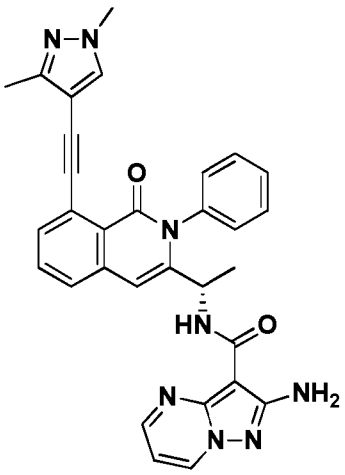
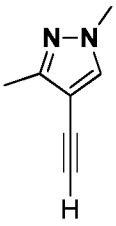
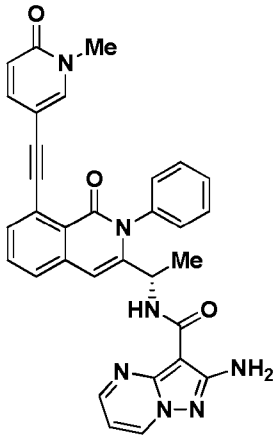
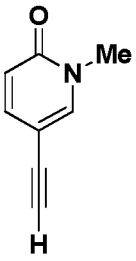
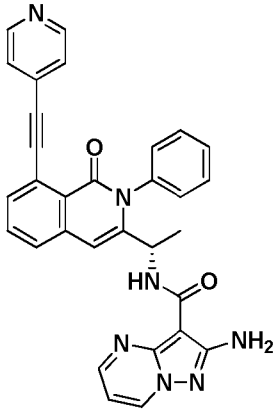
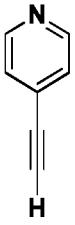
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 12			493.1 $[M+H]^+$
Compound 13			479.1 $[M+H]^+$
Compound 14			546.5 $[M+H]^+$
Compound 15			493.4 $[M+H]^+$

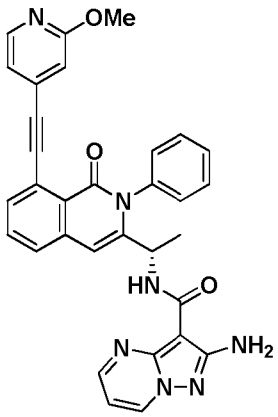
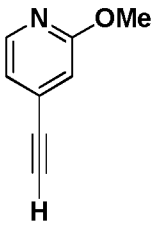
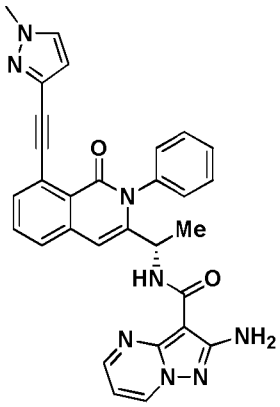
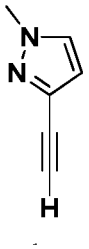
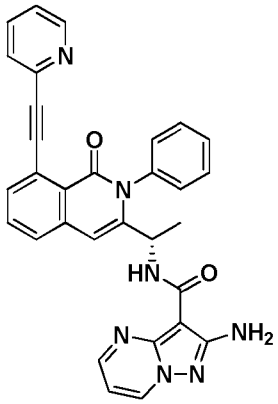
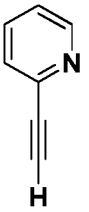
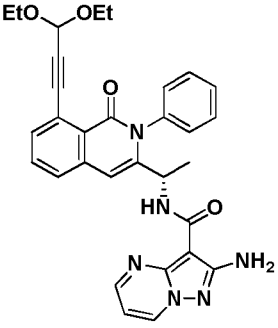
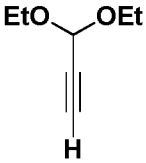
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 16			493.4 $[M+H]^+$
Compound 17			526.5 $[M+H]^+$
Compound 18		 Synthesized according to Method I	557.1 $[M+H]^+$

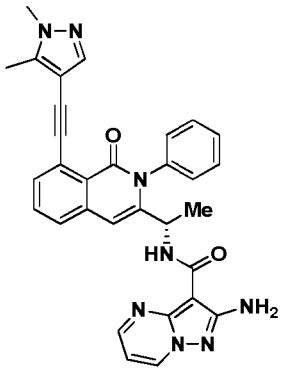
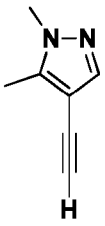
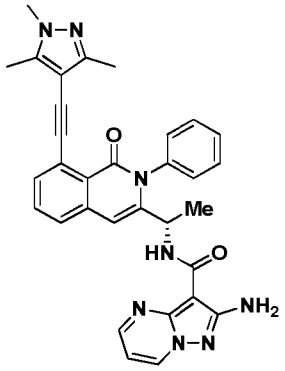
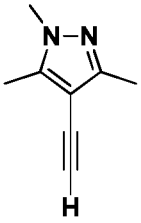
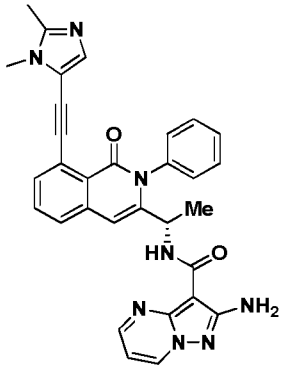
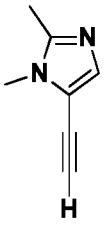
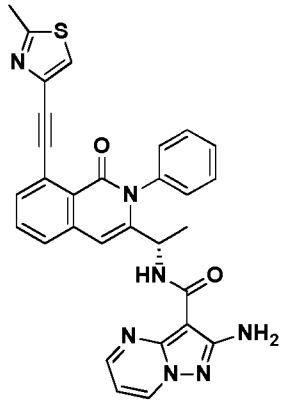
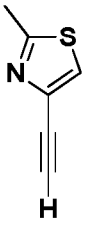
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 19		 Synthesized according to Method I	543.2
Compound 20		 Synthesized according to Method I	556.2 $[M+H]^+$
Compound 26			526.3 $[M+H]^+$

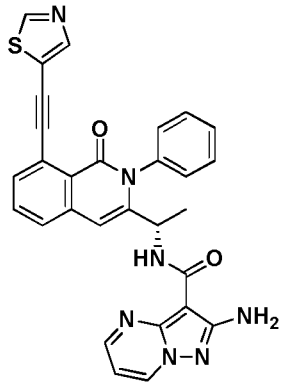
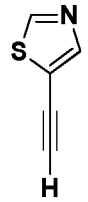
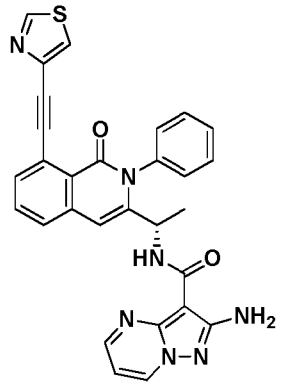
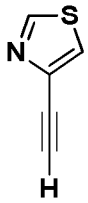
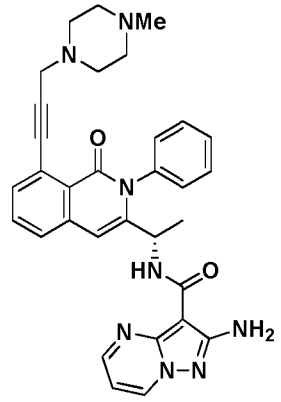
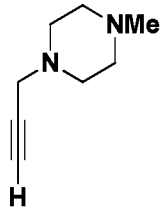
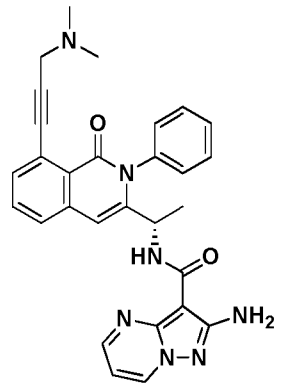
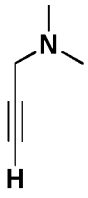
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 28		 Synthesized according to Method J	556.3 $[M+H]^+$
Compound 30		 Synthesized according to Method J	529.4 $[M+H]^+$
Compound 32			526.4 $[M+H]^+$
Compound 34			505.3 $[M+H(-OEt)]^+$

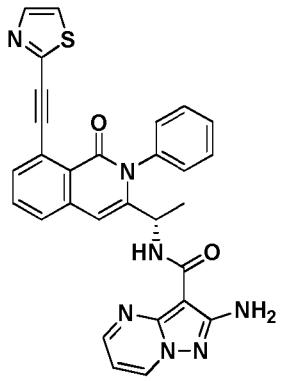
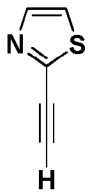
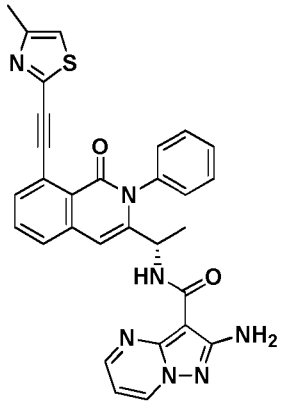
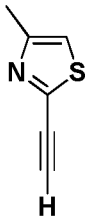
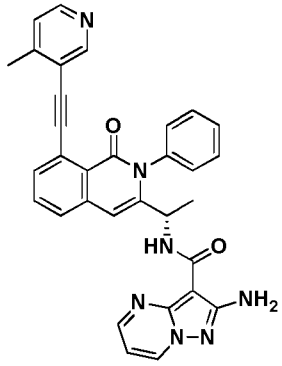
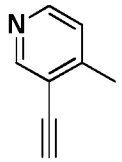
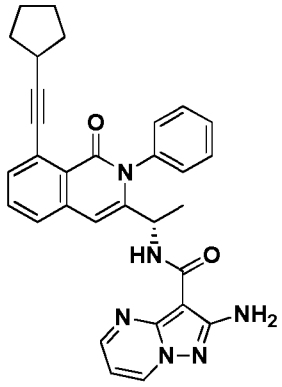
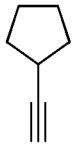
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 35		 Synthesized according to Method J	543.4 $[M+H]^+$
Compound 37		 Synthesized according to Method J	557.4 $[M+H]^+$
Compound 38		 Synthesized according to Method J	543.4 $[M+H]^+$
Compound 40		 Synthesized according to Method J	546.6 $[M+H]^+$

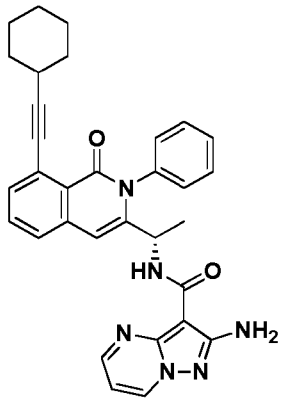
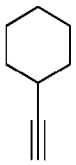
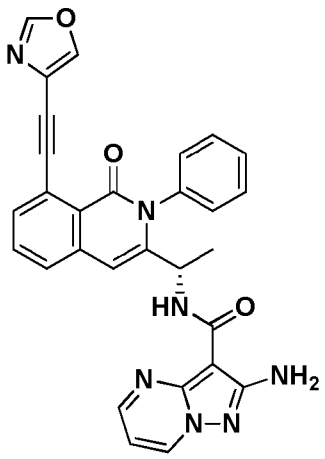
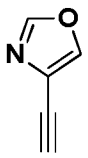
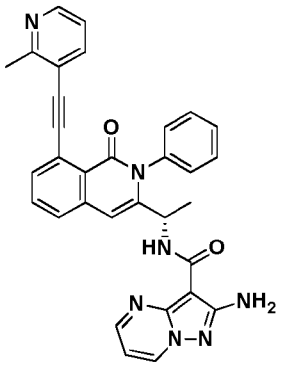
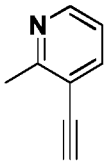
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 41		 Synthesized according to Method J	532.6 $[M+H]^+$
Compound 54		 Synthesized according to Method J	532.6 $[M+H]^+$
Compound 56		 Synthesized according to Method K	561.7 $[M+H]^+$
Compound 57			506.6 $[M+H]^+$

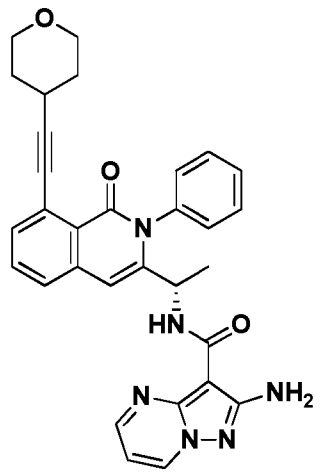
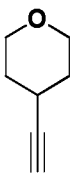
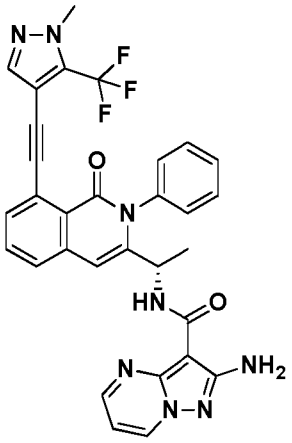
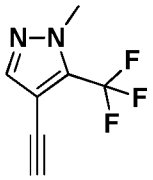
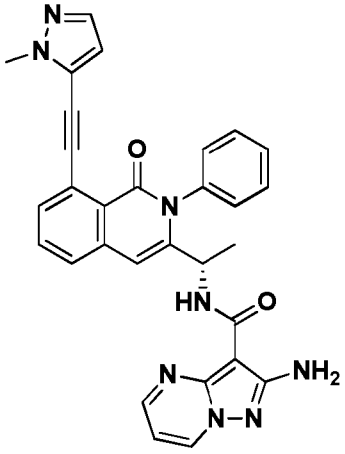
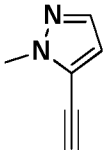
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 59		 Synthesized according to Method J	532.5 $[M+H]^+$
Compound 60		 Synthesized according to Method J	545.6 $[M+H]^+$
Compound 61		 Synthesized according to Method J	540.3 $[M+H]^+$
Compound 64			517.6 $[M+H]^+$

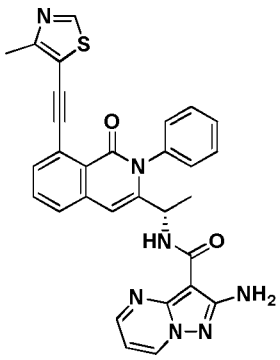
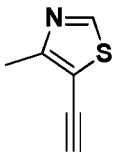
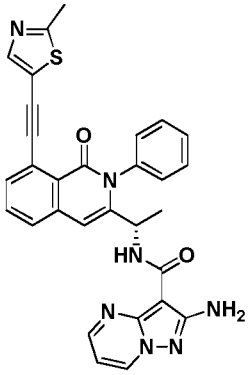
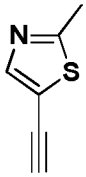
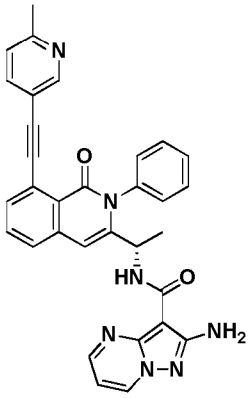
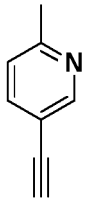
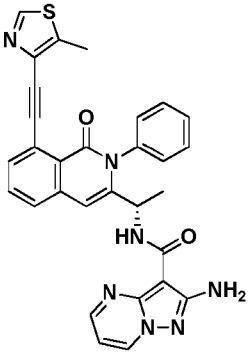
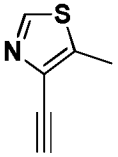
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 65			531.6 $[M+H]^+$
Compound 66		 Synthesized according to Method J	516.5 $[M+H]^+$
Compound 67		 Synthesized according to Method J	540.3 $[M+H]^+$

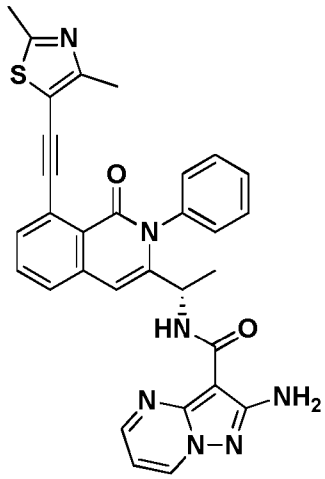
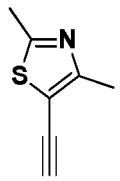
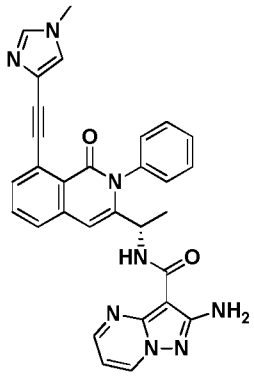
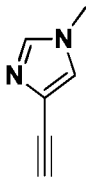
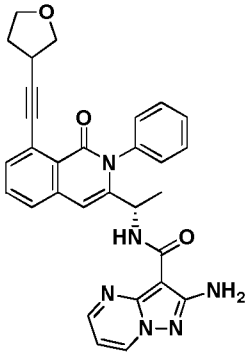
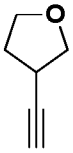
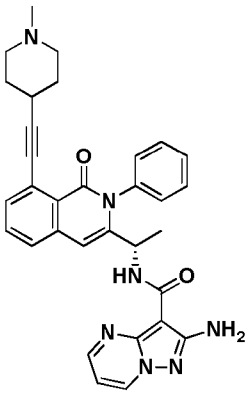
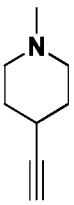
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Comound 27			533.5[M+H]$^+$
Compound 69		 Synthesized according to Method J	597.2 [M+H]$^+$
Compound 73		 Synthesized according to Method J	529.2 2 [M+H]$^+$

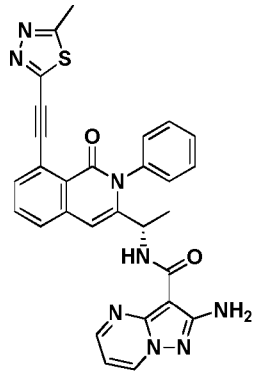
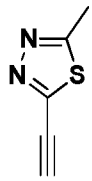
(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 75		 Synthesized according to Method J	546.2 $[M+H]^+$
Compound 76		 Synthesized according to Method J	546.2 $[M+H]^+$
Compound 77		 Synthesized according to Method J	540.3 $[M+H]^+$
Compound 78		 Synthesized according to Method J	546.2 $[M+H]^+$

(continued)

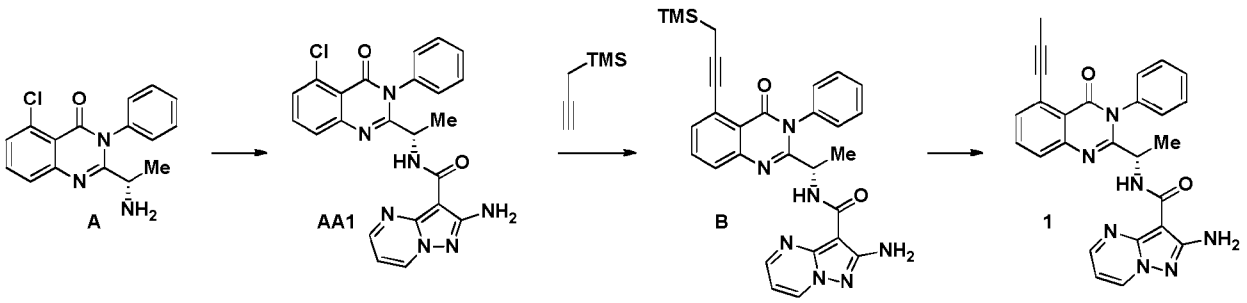
Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 79		 Synthesized according to Method J	560.1 $[M+H]^+$
Compound 81		 Synthesized according to Method J	529.0 $[M+H]^+$
Compound 84			519.4 $[M+H]^+$
Compound 85		 Synthesized according to Method J	546.5 $[M+H]^+$

(continued)

Compound no.	Structure	Alkyne	ESI-MS *m/z*
Compound 86		 Synthesized according to Method J	547.0 $[M+H]^+$

Comparative Example 2 (not covered by the wording of the claims)

[0491]

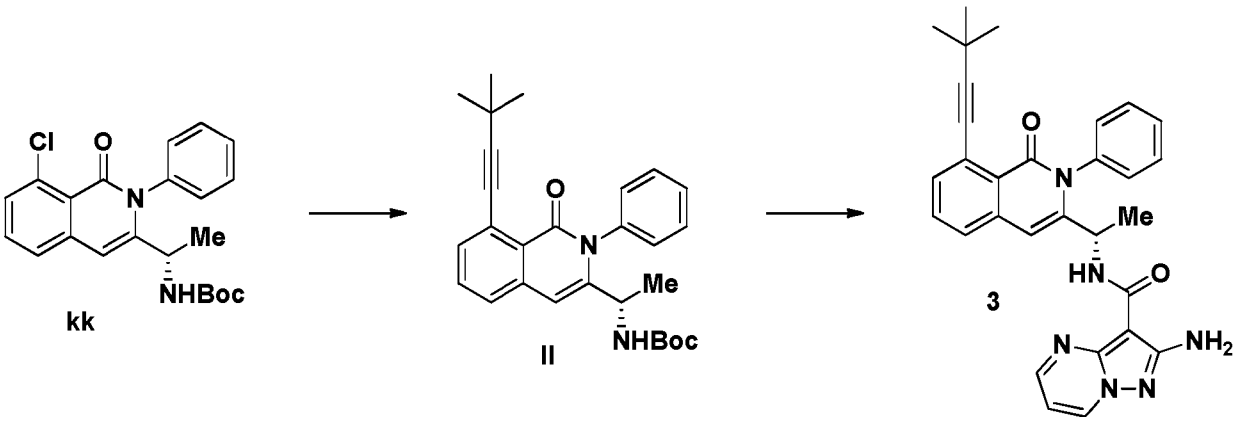


[0492] Compound **A** was prepared according to Method F. It was the converted to compound **AA1** using the analogous procedure for compound **B** in Example 1. Compound **1** was then prepared from compound **AA1** in two steps according to the following procedures: Compound **AA1** (0.55 mmol, 1.0 equiv), $PdCl_2(MeCN)_2$ (10 mol%), X-Phos (30 mol%) and cesium carbonate (2.6 equiv) were suspended in proprionitrile (4 mL). The mixture was bubbled with Ar for 25 min after which trimethyl(propargyl)silane (1.3 equiv) was added and the reaction was sealed and heated to 90 °C. The mixture was allowed to heat for 4.5h after which it was cooled and partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x). The organic layers were combined, dried over sodium sulfate and concentrated onto silica gel (2g). The crude material was then purified using flash silica gel chromatography (ISCO Combiflash Si-12g, gradient of 10-55% acetone/methylene chloride) to provide a mixture of compound **B** and deprotected compound 1.

[0493] The mixture (0.23 mmol, 1.0 equiv) was redissolved in anhydrous tetrahydrofuran (6 mL). TBAF in THF (1.0 M, 1.2 equiv) was added and the resulting mixture was stirred at RT for 45 min until complete conversion to compound 1 by TLC analysis. The reaction was then concentrated onto silica gel (1g) and purified by flash silica gel chromatography (Interchim Si-25g HP silicycle, gradient of 14-45% acetone/methylene chloride) to provide compound 1. ESI-MS *m/z:* 464.1 $[M+H]^+$.

Example 3

[0494]



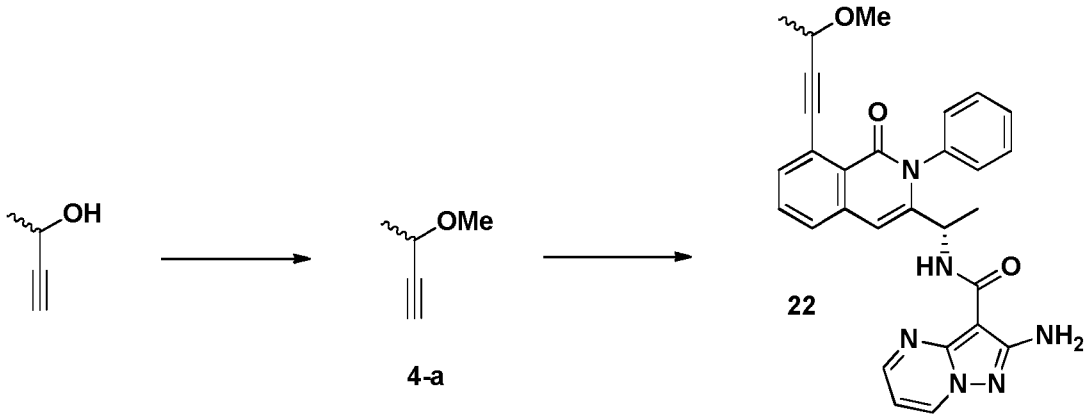
[0495] Compound kk was prepared from compound A (example 2) under standard Boc protection conditions. It was then converted to compound **11** using the analogous coupling procedure for compound **B** in Example 2 except that 3,3-dimethylbut-1-yne was used in place of triethylsilylacetylene to provide compound **11**

[0496] Compound **kk** was prepared from compound 1 in analogous fashion to compound gg in Example ZZ. It was then converted to compound **11** using the analogous procedure for compound **hh** in Example ZZ except that 3,3-dimethylbut-1-yne was used in place of triethylsilylacetylene to provide compound **11**.

[0497] Compound **11** (0.094 mmol, 1.0 equiv) was dissolved in anhydrous methylene chloride (2 mL). Trifluoroacetic acid (400 uL, 55 equiv) was added and the reaction was allowed to stir at RT for 2h until at which point there was no more SM by LC/MS analysis. The reaction was carefully quenched with sodium bicarbonate solution and the aqeous layer was extracted with methylene chloride (2x). The combined organic layers were dried with sodium sulfate and concentrated. The crude material was purified using reverse phase chromatography (Interchim, gradient of acetonitrile and water with 0.1% formic acid) to provide the free amine which was then coupled to 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid using Method D followed by Boc-deprotection again using the analogous conditions from Example 11 to provide the desired compound 3. ESI-MS *m/z:* 505.1 $[M+H]^+$.

Example 4

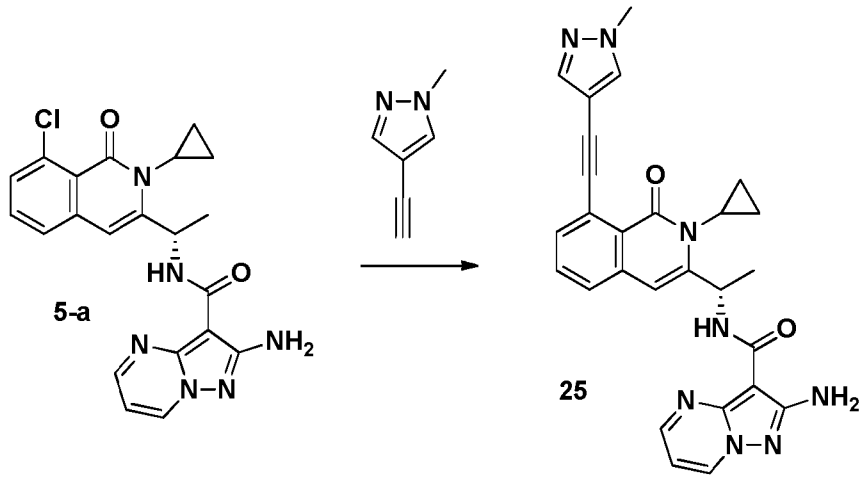
[0498]



[0499] A solution of 3-butyn-2-ol (10 mL, 128 mmol) in *N,N*-dimethylformamide (20 mL) was added over 30 minutes to a stirred slurry of sodium hydride (60% dispersion in mineral oil, (7.65 g, 2.5 equiv) in *N,N*-dimethylformamide (100 mL) at 0 °C under an argon atmosphere. After 30 min, dimethyl sulfate (1.5 equiv) was added over 30 min at 0 °C. The mixture was then stirred for 30 min at 0 °C after which acetic acid was slowly added (1.05 equiv) and the reaction was allowed to warm to room temperature while stirring for an additional 2h. The product was isolated from fractional distillation directly from the reaction mixture (58-63 °C) to provided ether **4-a** that was used directly in the next step. Compound **4-a** was then coupled to compound **A** using analogous Sonogashira conditions as in to Example 1 to generate compound 22. ESI-MS *m/z:* 507.5 $[M+H]^+$.

Example 5

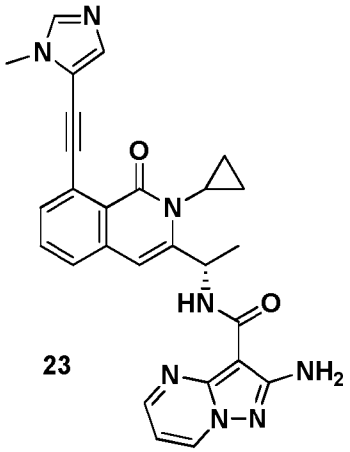
[0500]



[0501] Compound 25 was prepared in analogous fashion to compound B in Example 1. It was then coupled to 4-ethynyl-1-methyl-1H-pyrazole using the Sonogashira conditions in Example 1 to provide compound 25. ESI-MS *m/z:* 493.4 $[M+H]^+$.

Example 6

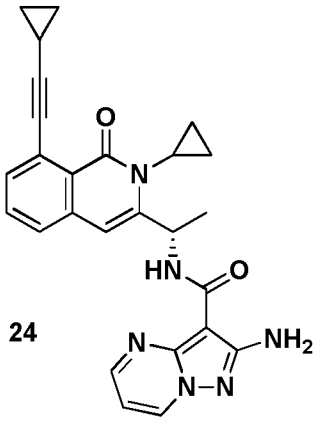
[0502]



[0503] Compound 23 was prepared in analogous fashion to compound 25 in Example 5 except that 5-ethynyl-1-methyl-1H-imidazole was used in place of 4-ethynyl-1-methyl-1H-pyrazole. ESI-MS *m/z:* 493.4 $[M+H]^+$.

Example 7

[0504]

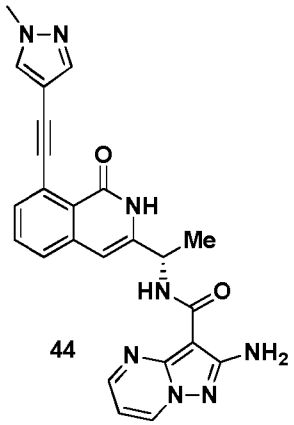


24

[0505] Compound 24 was prepared in analogous fashion to compound 25 in Example 5 except that ethynylcyclopropane was used in place of 4-ethynyl-1-methyl-1H-pyrazole. ESI-MS *m/z:* 453.4 $[M+H]^+$.

Example 8

[0506]

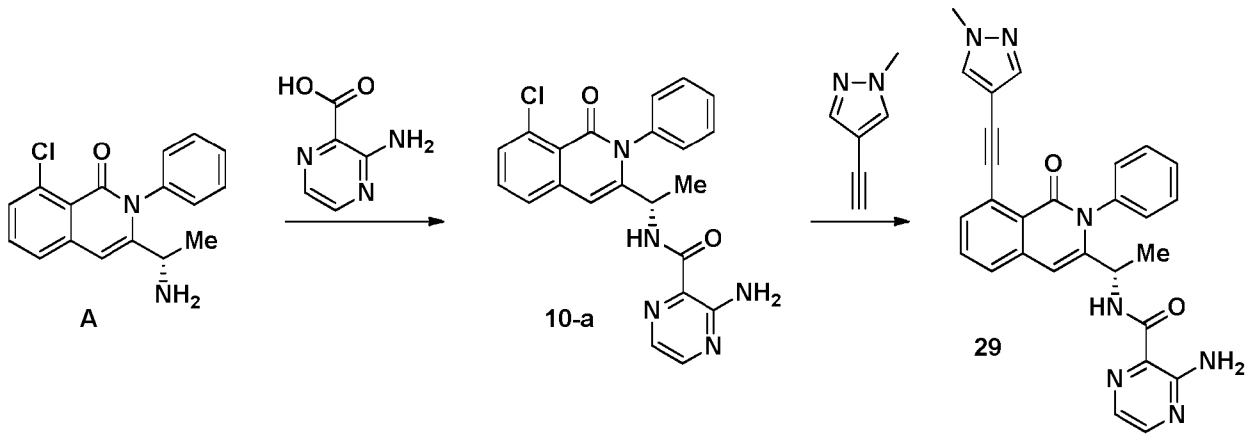


44

[0507] Compound 44 was isolated as a byproduct from Example 5. ESI-MS *m/z:* 453.4 $[M+H]^+$.

Example 10

[0508]

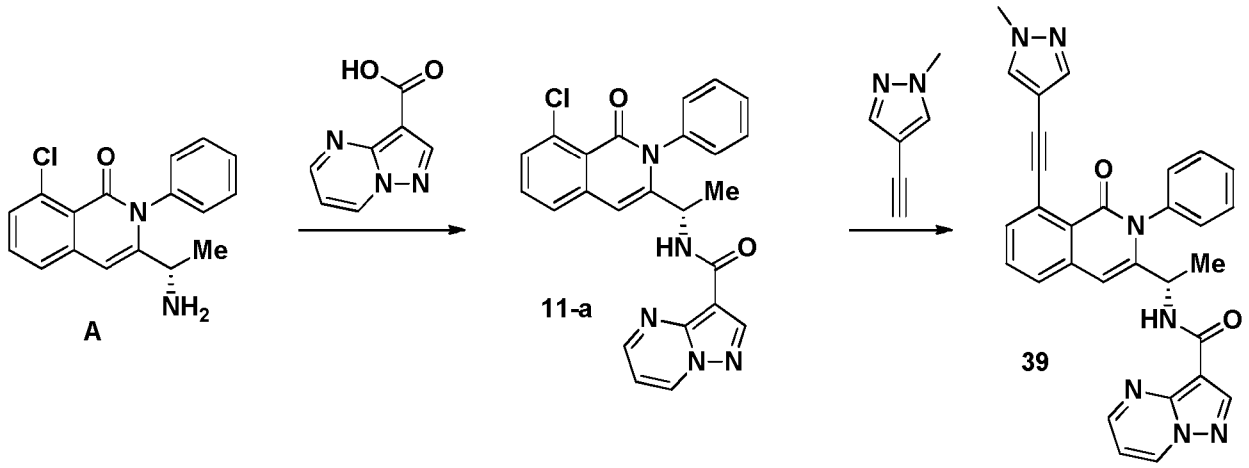


A 10-a 29

[0509] 3-Aminopyrazine-2-carboxylic acid was coupled to compound A using Method D to provide compound 10-a. It was then converted to compound 29 using analogous coupling conditions for the preparation of compound 4 in Example 1. ESI-MS *m/z:* 490.3 $[M+H]^+$.

Example 11

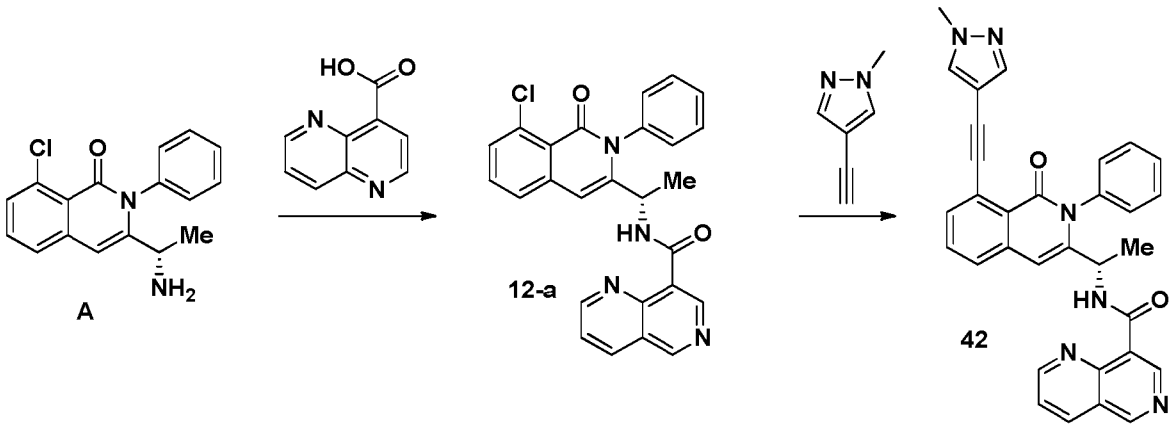
[0510]



[0511] Pyrazolo[1,5-a]pyrimidine-3-carboxylic acidwas coupled to compound A using Method D to provide compound **11-a.** It was then converted to comound 39 using analogous coupling conditions for the preparation of compound 4 in Example 1. ESI-MS *m/z:* 514.4 $[M+H]^+$.

Example 12

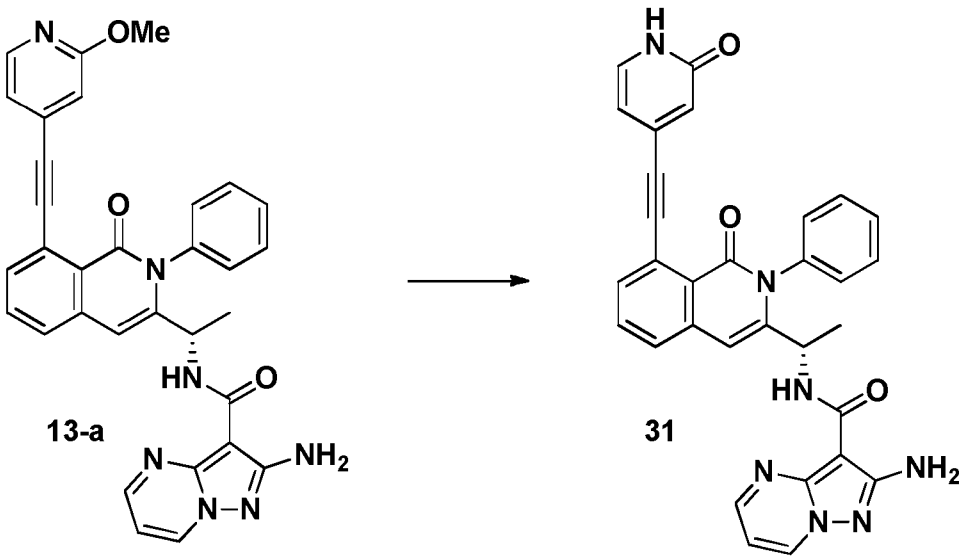
[0512]



[0513] 1,5-Naphthyridine-4-carboxylic acid was coupled to compound A using Method D to provide compound 12a. It was then converted to compound 42 using analogous coupling conditions for the preparation of compound 4 in Example 1. ESI-MS *m/z:* 525.3 $[M+H]^+$.

Example 13

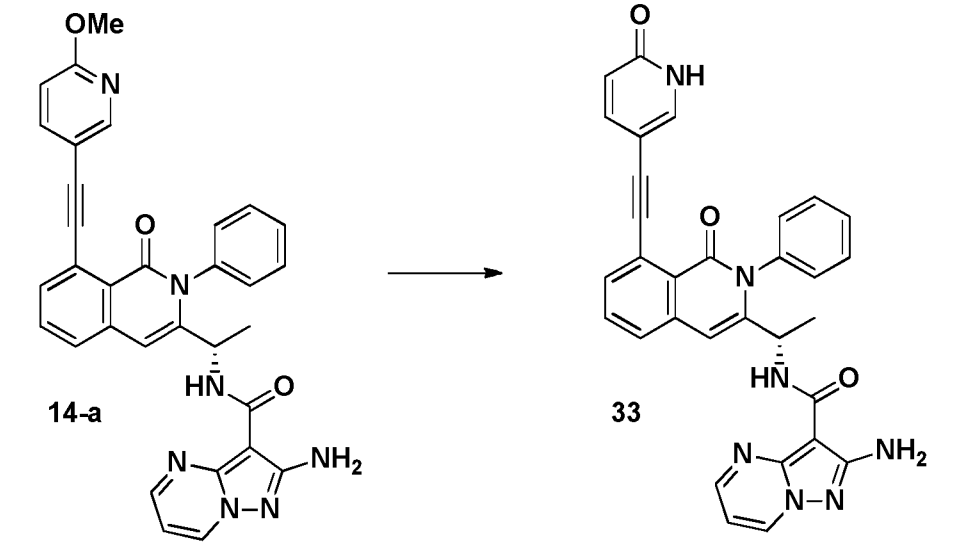
[0514]



[0515] Compound 13-a (0.058 mmol, 1.0 equiv) was dissolved in anhydrous acetonitrile (2 mL). Sodium iodide (1.5 equiv) was added followed by TMS-C1 (1.5 equiv) after which point the solution turned to a yellow suspension. The mixture was then heated to 65 °C for 5h after which there was no more starting material by LC/MS analysis. The reaction was allowed to cool and poured into water (4 mL) and stirred for 15 min after which it was partitionned between water and methylene chloride. The organic layer was when dried and concentrateed. The crude material was purified using reverse phase HPLC (Interchim, gradient of 10-90% acetonitrile/water with 0.1% formic acid) to provide desired compound 31. ESI-MS *m/z:* 542.4 $[M+H]^+$.

Example 14

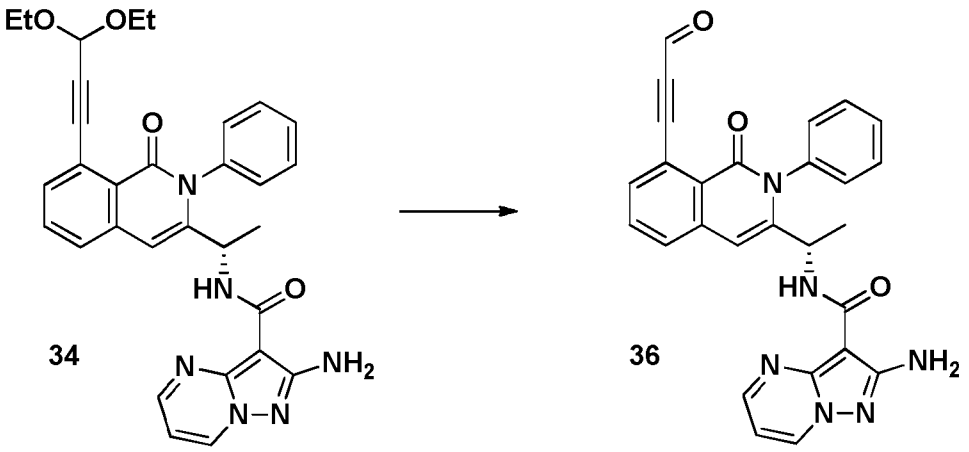
[0516]



[0517] Compound 33 was prepared from compound 14-a using the analogous conditions as in Example 13. ESI-MS *m/z:* 542.4 $[M+H]^+$.

Example 15

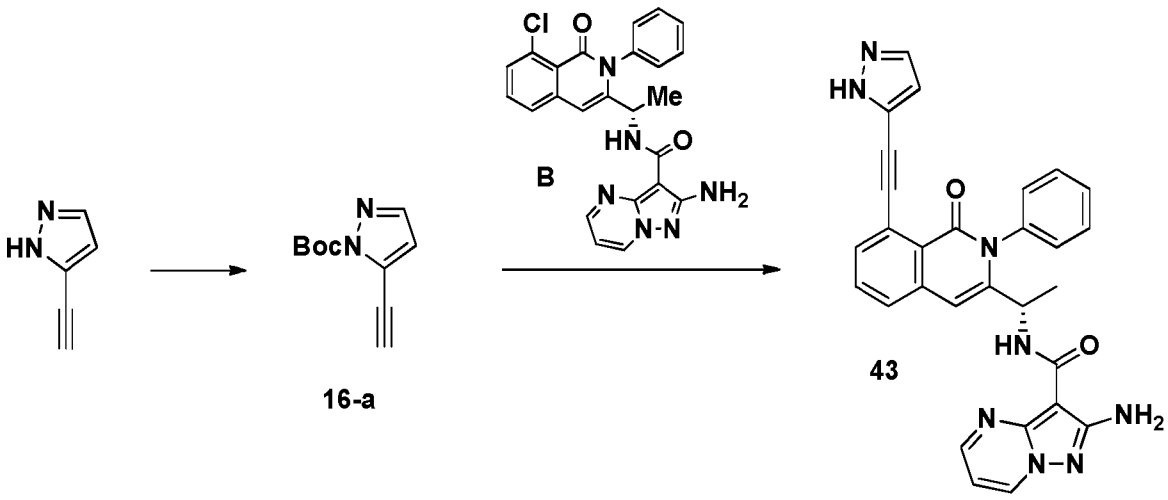
[0518]



[0519] Compound 34 was (0.47 mmol, 1.0 equiv) was dissolved in acetone (5 mL) and water (4 mL). *p*-Toluene sulfonic acid (25 mol%) was added and the cloudy mixture was heated to 50 °C. The mixture was then allowed to cool after which most of the solvent was removed under vacuum. The residue was then partitionned between methylene chloride and saturated sodium bicarbonate. The organic layer was separarted and adsorbed onto SiO_2 (3g) after which it was purified by flash silica gel chromatography (ISCO, 24g Si column, gradient of 25-100% ethyl acetate/hexanes) to provide the desired aldehyde 36. ESI-MS *m/z:* 477.2 $[M+H]^+$.

Example 16

[0520]

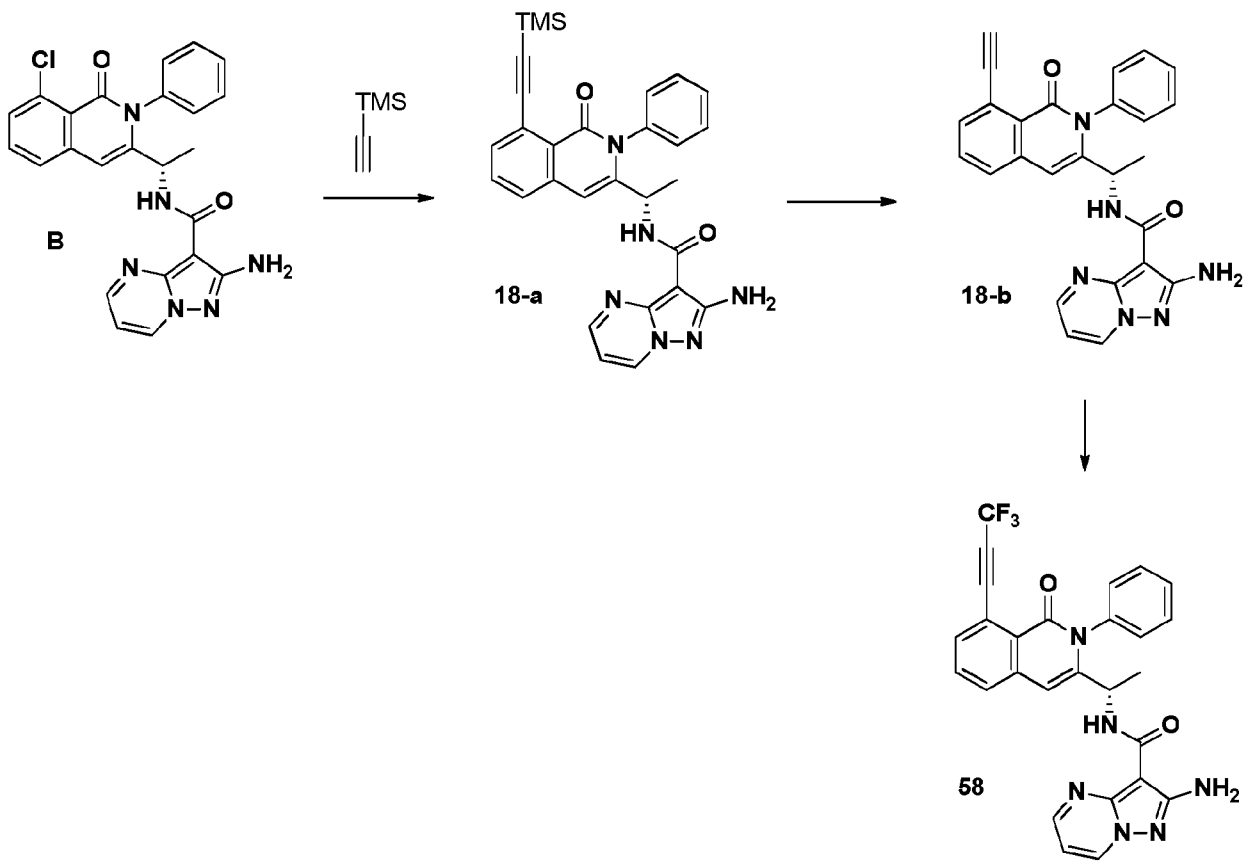


[0521] 5-Ethynyl-1H-pyrazole (1.1 mmol, 1.0 equiv) was dissolved in methylene chloride (10 mL). Triethylamine (3.0 equiv) and Boc anhydride (1.0 equiv) were then added and the reaction was allowed to stir for 2h. Water (100 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the water layer was washed with water (2 x 20 mL). The organic layers were dried over $MgSO_4$ and concentrated to provide alkyne **16-a** which was used directly in the next step.

[0522] A pressure flask (15 mL) was charged with compound B (0.22 mmol, 1.0 equiv), X-Phos (45 mol%), dichloro-bis(acetonitrile)Pd (15 mol%), and cesium carbonate (1.1 equiv) under a flow of N_2. Propionitrile (3 mL) was added and the solution was bubble with Ar for 1 min. Alkyne **16-a** (2.5 equiv) was then added followed by Boc anhydride (1.0 equiv) and the reaction was sealed and heated to 100 °C for 1.h. The reaction was then filtered and concentrated. The residue was redissolved in methylene chloride (3 mL) after which trifluoroacetic acid (800 uL) was added and the the mixture was stirred for 1h. The reaction was then concentrated onto silica gel and purified by flash silica gel chromatography (gradient 0-30% methanol /methylene chloride) to provide compound 43. ESI-MS *m/z:* 515.4 $[M+H]^+$.

Example 18

[0523]



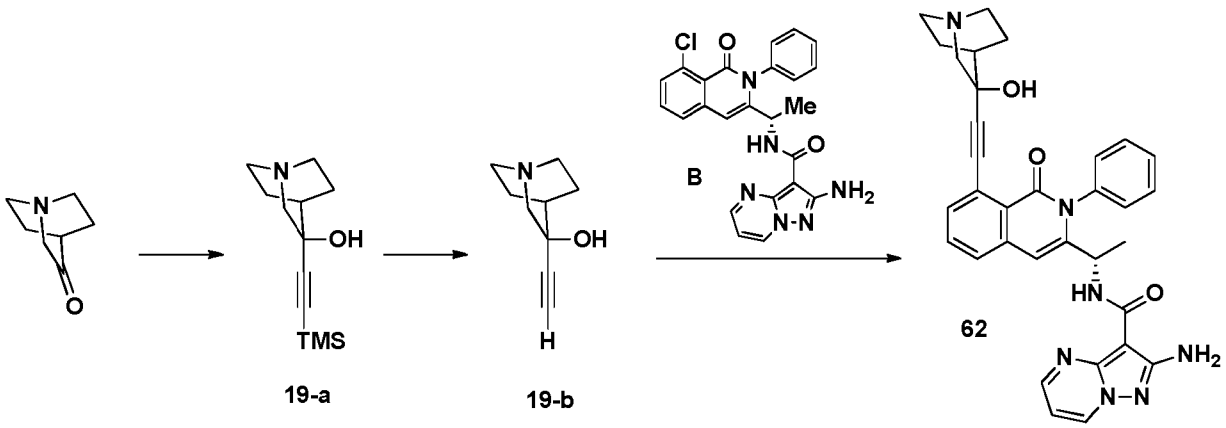
[0524] A sealed tube (30 mL) was charged with compound B (0.69 mmol, 1.0 equiv), dichlorobis(acetonitrile)palladium (10 mol%), X-Phos (30 mol%) and cesium carbonate (1.5 equiv). Acetonitrile (10 mL) was added followed by the additional of ethynyltrimethylsilane (0.4 mL) and the mixture was purged with Ar for 1 min. The reaction was then sealted and heated in an oil bath to 85 °C. After 45 min, an additional aliquot of ethynyltrimethylsilane (1.0 mL) was added and reheated to 75 °C for 14h after which there was no more starting material by LC/MS analysis. The mixture was filtered and concentrated onto silica gel and purified by flash silica gel chromatography (Combiflash, 12g column, gradient of 0-5% methanol/methylene chloride) to provide compound **18-a.**

[0525] Compound **18-a** (0.57 mmol, 1.0 equiv) was the dissolved in tetrahydrofuran (4 mL). A solution of TBAF in tetrahydrofuran (0.8 mL, 1.0 M) was added and the mixture was stirred at RT for 1h at which point the deprotected product was observed as the desired peak by LC/MS analysis. The solution was concentrated onto silica gel and purified using flash silica gel chromatography (Combiflash, 12g column, gradient of 0-5% methanol/methylene chloride) to provide compound **18-b.**

[0526] An oven dried RBF with a stir bar was charged with CuI (0.34 mmol, 1.0 equiv), 1,10-phenanthroline (1.0 equiv) and KF (1.0 equiv). Dry *N,N*-dimethylformamide (2 mL) was added and the mixture was stirred for 15 min under an atmosphere of air. Trimethyl(trifluoromethyl)silane (5.0 equiv) was then added and the mixture was heated to 100 °C under an air atmosphere. A solution of compound **18-b** (1.0 equiv in 2 mL N,N-dimethylformamide) was added over the course of 4h using a syringe pump. Following the completion of compound **18-b** addition, the reaction was stirred for an additional 1.5h at 100 °C. At this point the reaction was allowed to cool after which water (100 mL) was added and the mixture was extracted with methylene chloride (3x). The combined organics were washed with water, dried over sodium sulfate and concentrated onto silica gel after which the material was purified by flash silica gel chromatography (Combiflash, 4g column, gradient of 0-10% methanol/methylene chloride). The crude material was further purified by reverse phase HPLC (Interchim, gradient of 0-10% acetonitrile:water with 0.1 % formic acid to provide the desired alkyne **58.** ESI-MS *m/z:* 517.5 $[M+H]^+$.

Example 19

[0527]



[0528] 3-Quinuclidone hydrochloride (9.6 mmol, 1.0 equiv) was suspended in methylene chloride (30 mL) and potassium carbonate solution was added (1.0 M, 16 ml). The mixture was stirred for 30 min after which the organic later was collected and the aqueous layer was washed with methylene chloride (3x20 mL), dried over sodium sulfate, filtered and concentrated to provide the corresponding free base.

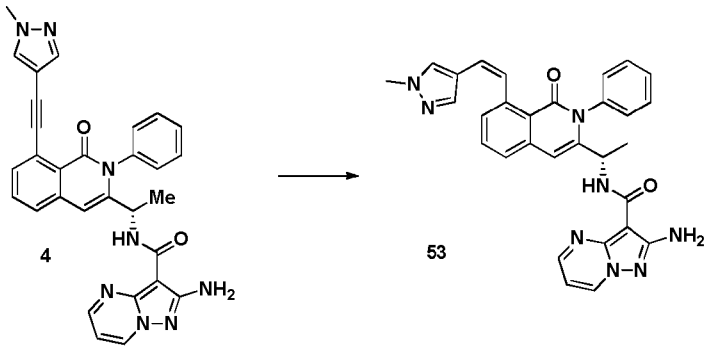
[0529] A solution of ethynyltrimethylsilane (10.6 mmol, 1.1 equiv) in tetrahydrofuran (10 mL) was cooled to -10 oC. *n*-Butyl lithium (2.5 M in THF, 1.15 equiv) was added over 7 min. The reaction was stirred at -10 °C for 30 min after which it was cooled to -78 °C. 3-Quinuclidone (1.0 equiv in 20 mLTHF) was added to the flask over a period of 20 min, stirred for 15 additional min after which the cooling bath was removed and the reaction was alllowed to stir at 23 °C for 15h. The mixture was then quenced with saturated ammonium chloride (50 mL) and extracted with ethyl acetate (5 x 25 mL). The combined organic layers were then washed with water (1 x 20 mL) and brine (1 x 20 mL), dried over sodium sulfate and concentrated under reduced pressure to provide alkyne **19-a** which was used directly in the next step.

[0530] Compound **19-a** (7.7 mmol, 1.0 equiv) was dissolved in methanol (17 mL) and treated with potassium carbonate (1.05 equiv). The reaction was allowed to stir at room temperature for 4h after which it was filtered through celite, washing with 10% methanol in methylene chloride. The filtrates were concentrated under reduced pressure to half the volume and filtered again after which they were concentrated completely under reduced pressure. The material was then redissolved in chloroform (30 mL) and washed with 50% saturated brine (10 mL). The aqueous layer was extracted with chloroform (3 x 20 mL). The combined organic layers were then washed with brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure to provide compound **19-b.**

[0531] An oven dried sealed tube was charged with dichlorobis(acetonitrie)palladium (15 mol%), X-Phos (45 mol%), and cesium carbonate (1.2 equiv) followed by propionitrile (5 mL). Compound B (0.22 mmol, 1.0 equiv) was added and the reaction was degassed with Ar for 15 min. Alkyne **19-b** (3.0 equiv) was added as a solid and the mixture was purged for an additional 1 min with Ar. The flask was then sealed and heated to 100 °C for 2.5 h after which there was no more starting material by LC/MS analysis. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure and adsorbed onto a 1:4 ratio of Si-Triamine and silica gel (1.5g) after which it was purified using flash silica gel chromatography (Interchim, 12g Si column, gradient of 0-20% 1M ammonia in methanol/methylene chloride) to provide the desired compound 62. ESI-MS *m/z:* 574.6 $[M+H]^+$.

Example 28

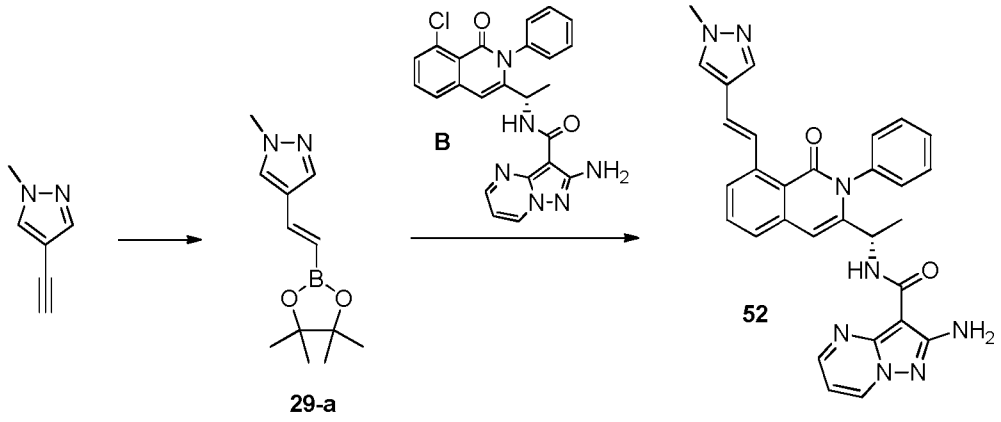
[0532]



[0533] Compound 4 (0.12 mmol, 1.0 equiv) was dissolved in a mixture of ethanol and ethyl acetate (20 mL, 3:1 v/v). Palladium on carbon (19 mg, 10% Pd) was added and the reaction was placed under an atmosphere of H2. The mixture was stirred at RT for 41h after which it was filtered through a filter disk, concentrated and purified by flash silica gel chromatography (Combiflash, 4g Si column, gradient of 0-5% methanol/methylene chloride) to provide alkene 53. ESI-MS *m/z:* 531.6 $[M+H]^+$.

Example 29

[0534]

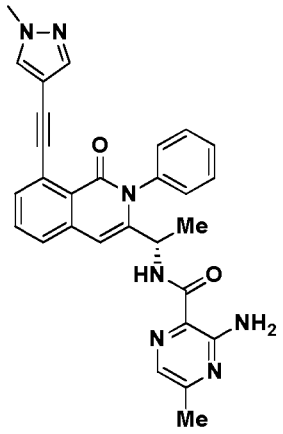


[0535] 4-Ethynyl-1-methyl-*1H*-pyrazole (1.8 mmol, 1.0 equiv) and pinacolborane (5.0 equiv) were combined in toluene (8 mL) in a RBF under Ar. Carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) (10 mol%) was added and the reaction was heated to 50 °C for 1.5h after which there was no more starting material by LC/MS analysis. The solvent was evaporated and the crude residue was transferred to a separatory funnel with ethyl acetate (10 mL) and washed with saturated sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, concentrated and purified using flash silica gel chromatography (gradient 10-40% ethyl acetate/hexanes) to provide alkene **29-a.**

[0536] Compound **B** (0.22 mmol, 1.0 equiv), $PdCl_2(Amphos)_2$ (10 mol%) and sodium carbonate (2.0 equiv) were charged to a 4 mL vial under an Ar atmosphere. A solution of compound **29-a** in dioxane/water (1.5 equiv, 2 mL solvent, 4:1 v/v) was added and the reaction was stirred at RT for 5 min under Ar before heating to 85 °C for 1h. The reaction was then allowed to cool, diluted with methylene chloride (15 mL) and washed with water (15 mL). The aqueous layer was then washed with additional methylene chloride (2 x 15 mL). The organic layers were combined and then washed with water (30 mL), brine (20 mL), dried over sodium sulfate and concentrated to provide crude material which was first purified by flash silica gel chromatography (Interchim Si-12g, gradient of 0-5% methanol/methylene chloride) followed by purification using reverse phase HPLC (Interchim C18-Sunfire column, acetonitrile/water/0.1% formic acid) to provide compound **52.** ESI-MS *m/z:* 531.4 $[M+H]^+$.

Example 30

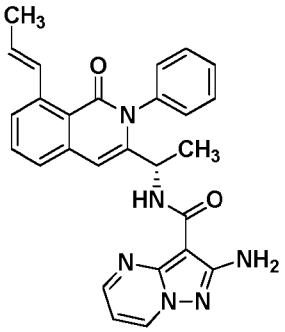
[0537]



[0538] Compound 68 is prepared according to the methods described herein. ESI-MS *m/z:* 504.2 $[M+H]^+$.

Example 31

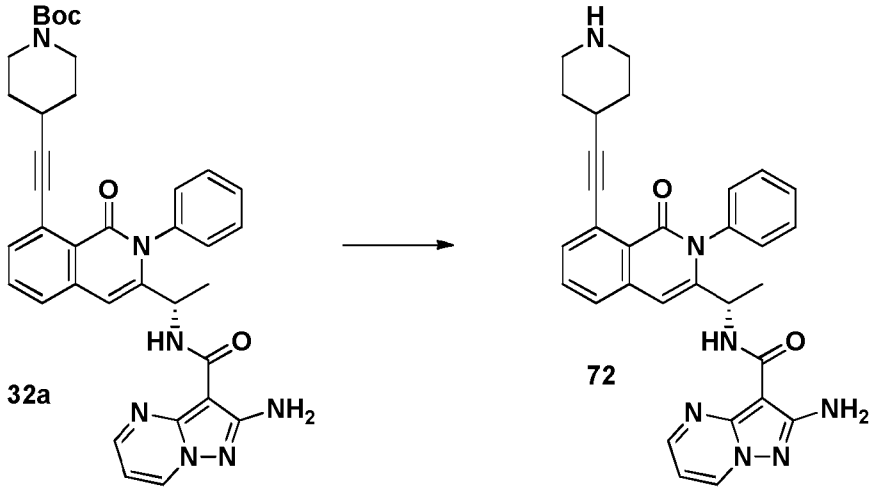
[0539]



[0540] Compound B and *trans*-1-propen-1-ylboronic acid were coupled using the analogous Suzuki coupling conditions in Example 29 to provide Compound 70. ESI-MS *m/z:* 465.2 $[M+H]^+$.

Example 32

[0541]

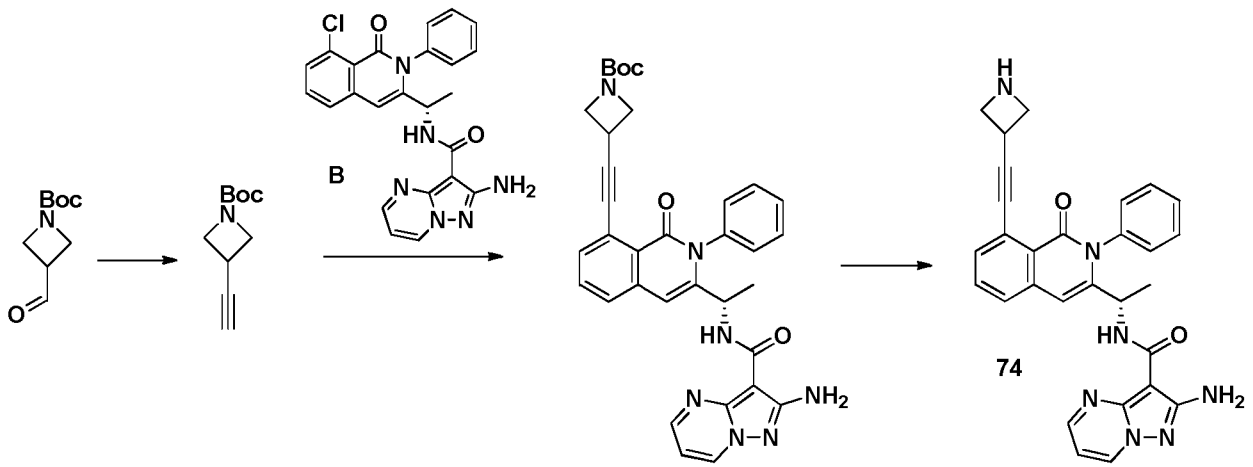


[0542] Compound Band 4-ethynylpiperidine-1-carboxylic acid tert-butyl ester were coupled using the Sonogashira

coupling conditions in Example 1 to provide compound 32a. Compound 32a was then dissolved in methylene chloride (.007 M) followed by the addition of trifluoroacetic acid (10 equiv). The reaction was allowed to stir for 2h at RT after which it was concentrated under vacuum. The residue was treated with excess saturated sodium bicarbonate. The resulting residue was isolated via vacuum filtration and washed with excess water to provide Compound 72. ESI-MS *m/z:* 532.6 $[M+H]^+$.

Example 33

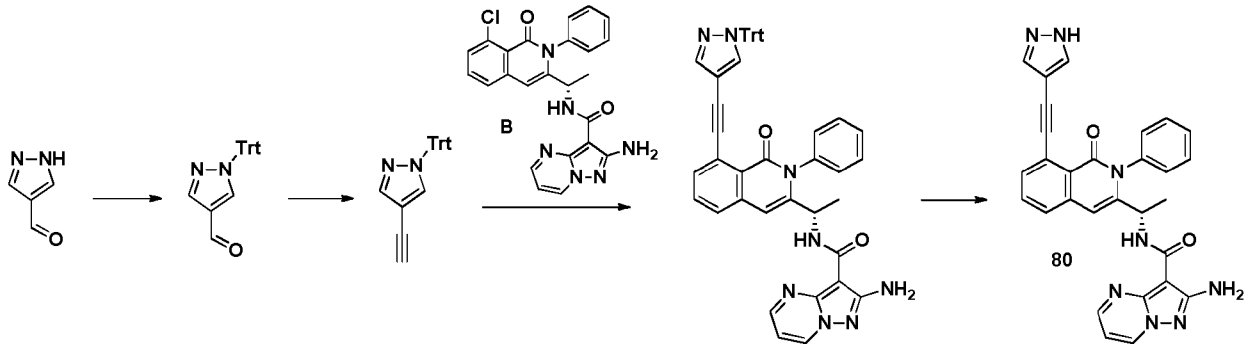
[0543]



[0544] Compound 74 was prepared in 3 steps according to the following procedures: *tert*-Butyl 3-formylazetidine-1-carboxylate was converted to *tert-butyl* 3-ethynylazetidine-1-carboxylate according to Method J. It was then coupled to compound B and subsequently deprotected in analogous fashion to the synthesis of Compound 72 in Example 32.ESI-MS *m/z:* 504.5 $[M+H]^+$.

Example 34

[0545]

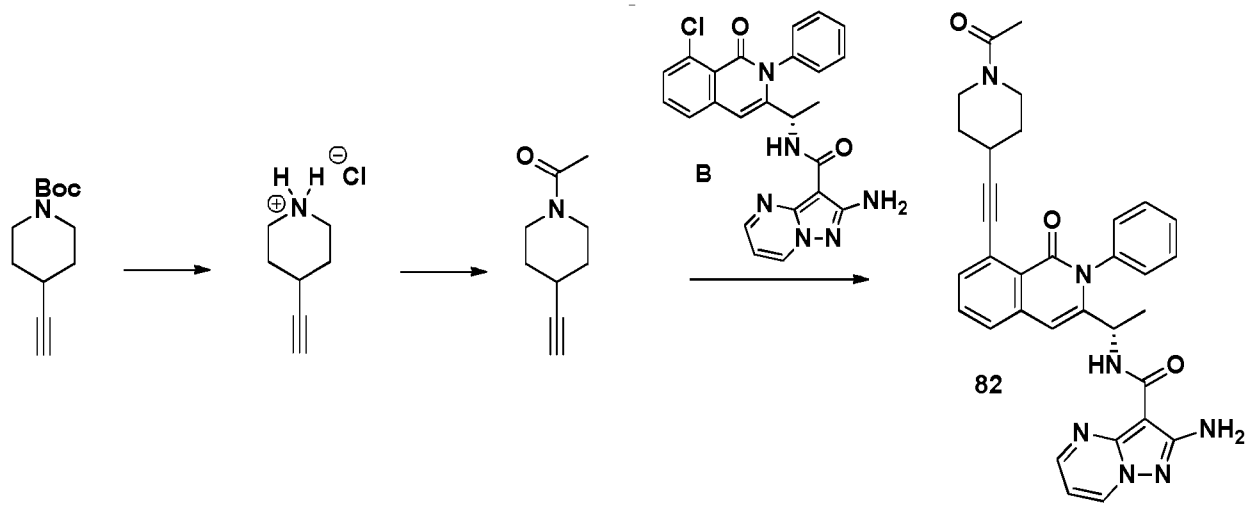


[0546] Compound 80 was prepared in 4 steps from 1H-pyrazole-4-carbaldehyde according to the following procedures: 1H-pyrazole-4-carbaldehyde (2.1 mmol, 1.0 equiv) was dissolved in 20 mL methylene chloride followed by the addition of triethylamine (3.0 equiv) and trityl chloride (1.0 equiv). The reaction was stirred at RT for 1h after it was quenched with water (1mL) and extrated with methylene chloride. The organic layers were concentrated and purified using flash silica gel chromatography (gradient 0-30% methanol/methylene chloride with 0.5% triethylamine). 1-Trity -*1H*-pyrazole-4-carbaldehyde was then converted to it's corresponding alkyne using Method J after which it was coupled to compound B using the analogous coupling conditions in Example 1. The resulting compound was then deprotected under standard triflouroacetic acid in methylene chloride deprotection conditions after which it was concentrated and purified using flash silica gel chromatography (ISCO, gradient 0-5% methanol/methylene chroride with 0.05% triethylamine and then repurified using reverse-phase HPLC (Interchim C18-Sunfire column, gradient of acetonitrile/water with 0.01% formic acid)

to provide compound 80. ESI-MS *m/z:* 515.0 $[M+H]^+$.

Example 35

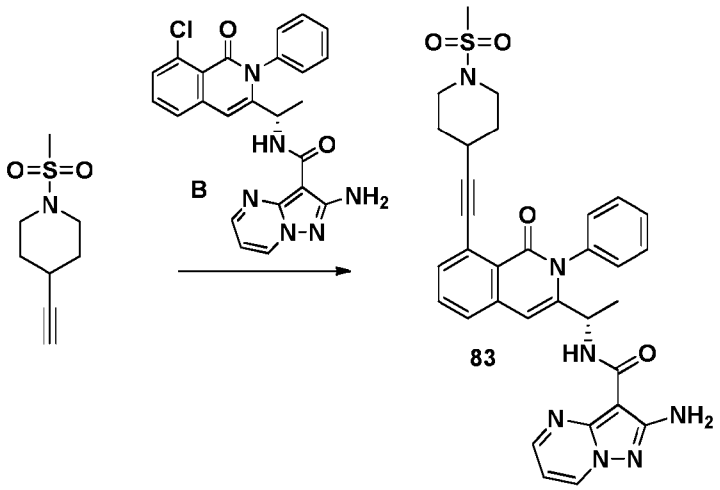
[0547]



[0548] Compound 82 was prepared in 3 steps according to the following procedures: N-Boc-4-ethynylpiperidine (3.8 mmol) was dissolved in dioxane (10 mL) and HCl in dioxane (4M, 5.0 equiv) was added. The reaction was allowed to stir at RT for 22h. The mixture was concentrated under reduced pressure, diluted with 10 mL dioxane and reevaporated under reduced pressure. Diethylether (20 mL) was then added and the mixture was revaporated to provide the HCl salt that was used directly in the next step. A suspension of the HCl salt (1.05 mmol, 1.0 equiv) in methylene chloride (1 mL) was cooled to 0-5 oC in an ice bath. Hunig's base (3.0 equiv) was added and then after a minute of stirring acetic anhydride (2.0 equiv) was added. The mixture was allowed to stir for 1h after which there was no more starting material by TLC analysis. The reaction was then diluted with methylene chloride (5 mL), washed with 5% citric acid (1x2 mL), water (1x2 mL) dried over sodium sulfate, and evaporated under reduced pressure. The crude residue was purified using flash silica gel chromatography (ISCO, 4g column, 0-50% ethyl acetate in methylene chloride) to provide *N*-acetyl-4-ethynylpiperidine which was coupled directly to compound B using the analogous Sonogashira coupling conditions in example 1 to provide compound 82. ESI-MS *m/z:* 574.5 $[M+H]^+$.

Example 36

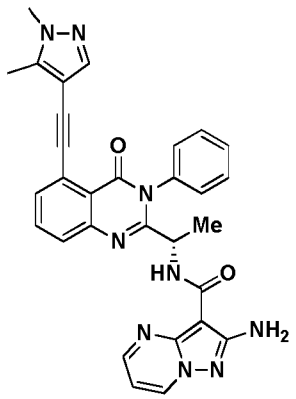
[0549]



[0550] A suspension of 4-ethynyl piperidine HCl (1.1 mmol, 1.0 equiv) was suspended in methylene chloride (1 mL) and cooled to 0-5 °C in an ice bath. Hunig's base (3.0 equiv) was added and then after a minute of stirring methanesulfonyl chloride (2.0 equiv) was added and the reaction was allowed to stir for 1h after which there was no more starting material by LC/MS analysis. The mixture was then diluted with methylene chloride (5 mL) washed with 5% citric acid (1x2 mL), water (1x2 mL), dried over sodium sulfate and concentrated. The crude residue was purified using flash silica gel chromatography (ISCO, 12g Si column, gradient of 0-10% ethyl acetate/methylene chloride) to provide *N*-methanesulfonamide-4-ethynylpiperidine which was coupled directly to compound B using the analogous Sonogashira coupling conditions in example 1 to provide compound 83. ESI-MS *m/z:* 610.6 $[M+H]^+$.

Example 37

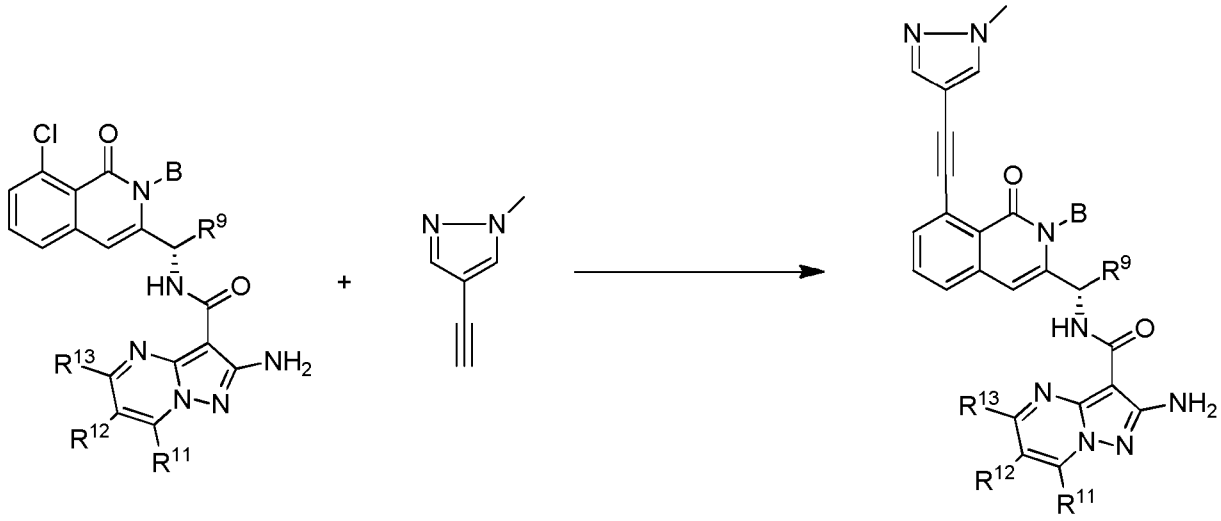
[0551]



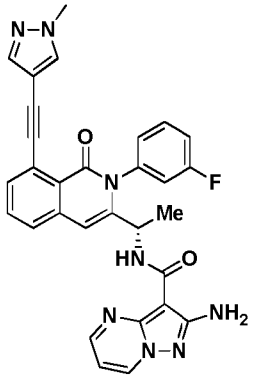
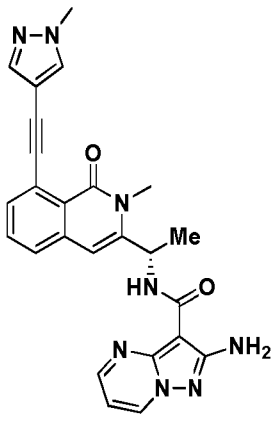
[0552] Compound 88 was prepared in analogous fashion as compound 21 in example 9 except that 4-ethynyl-1,5-dimethyl-1H-pyrazole was used in place of 4-ethynyl-1-methyl-1H-pyrazole. A suspension of (S)-2-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (146 mg, 0.317 mmol), Cesium carbonate (198 mg, 0.608 mmol, 2 eq.), Dichlorobis(acetonitrile)palladium (II) (15 mg, 0.058 mmol, 0.2 eq.) and Xphos (87 mg, 0.182, 0.6 eq.) in propionitrile (2 mL) was bubbled with argon for 5 minutes. The mixture was charged with 4-ethynyl-1,5-dimethyl-1H-pyrazole (73 mg, 0.6 mmol, 2 eq.), heated to 95 oC and stirred for 2 hr. The resulting mixture was cooled to RT, partitioned between Ethyl acetate and water. The organic phase was separated, washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. . The residue was purified with silica gel chromatography using a gradient of DCM and MeOH to afford (S)-2-amino-N-(1-(5-((1,5-dimethyl-1H-pyrazol-4-yl)ethynyl)-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. ESI-MS *m/z:* 544.2 $[M+H]^+$.

Example 41

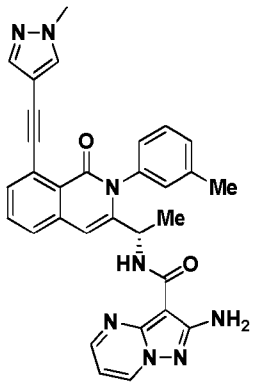
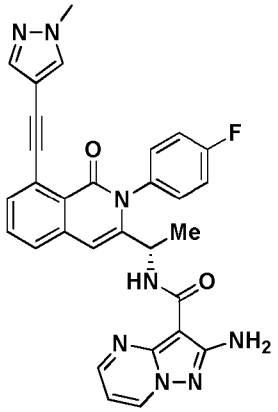
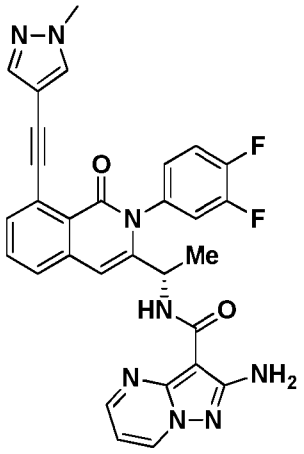
[0553] Compounds 93-108 were prepared according to the procedure below.



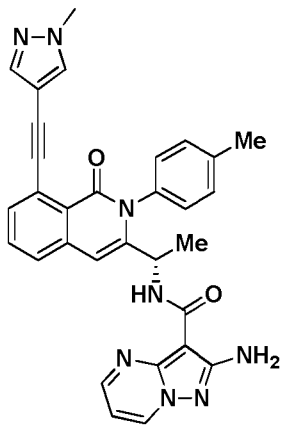
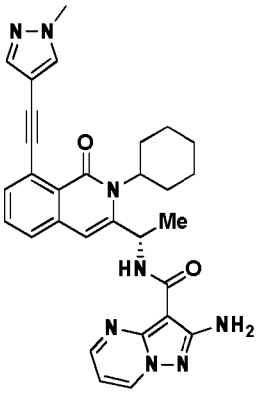
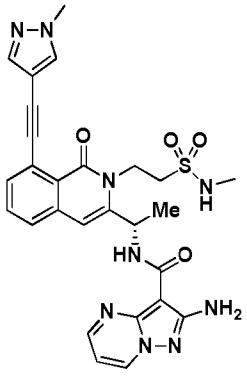
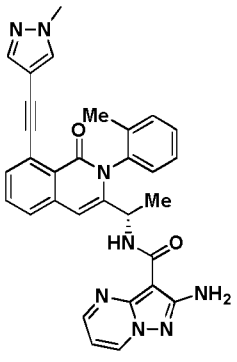
[0554] A suspension of aryl chloride (0.03-0.06 mmol), cesium carbonate (1.2 eq.), dichlorobis(acetonitrile)palladium (II) (0.05 eq.) and Xphos (0.15 eq.) in acetonitrile (2 mL) was bubbled with argon for 5 minutes. The mixture was charged with 4-ethynyl-1-methyl-1H-pyrazole (2 eq.), heated to 75 °C and stirred for 6 hr. The resulting mixture was cooled to RT, partitioned between ethyl acetate and water. The organic phase was separated, washed with saturated aqueous sodium chloride solution, dried with sodium sulfate and concentrated. The residue was purified on semi-prep HPLC (C-18) using a gradient of ACN/Water/Formic acid (9.9/90/0.1% to 49.9/50/0.1%) to afford the desired compound (confirmed by LCMS).

Compound no	Structure	ESI-MS *m/z* [M+H]$^+$
93		547.2
94		467.2

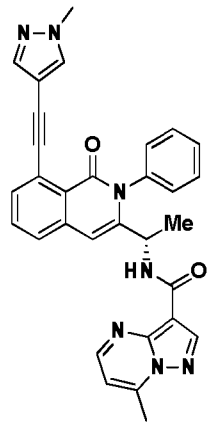
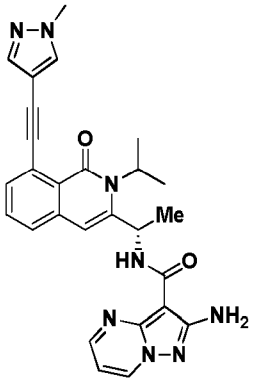
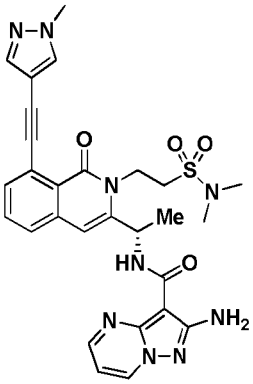
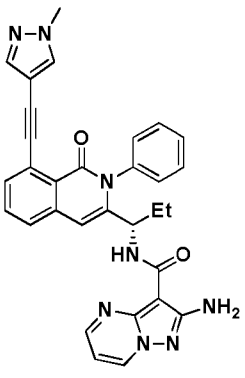
(continued)

Compound no	Structure	ESI-MS *m/z* [M+H]+
95		543.2
96		547.2
97		565.2

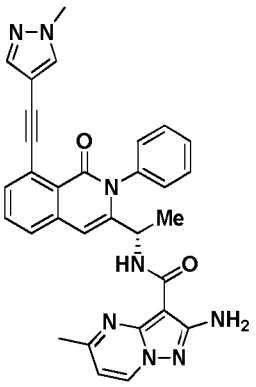
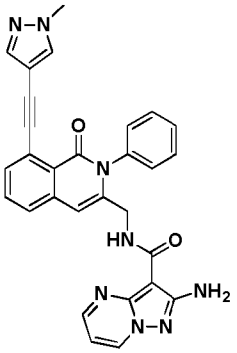
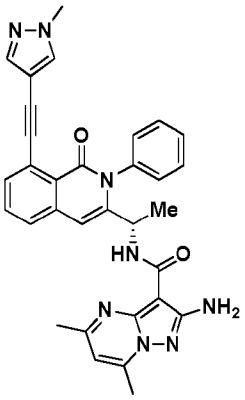
(continued)

Compound no	Structure	ESI-MS *m/z* $[M+H]^+$
98		543.2
99		535.3
100		574.2
101		543.2

(continued)

Compound no	Structure	ESI-MS *m/z* $[M+H]^+$
102		543.2
103		495.2
104		588.2
105		543.3

(continued)

Compound no	Structure	ESI-MS *m/z* [M+H]$^+$
106		543.3
107		515.2
108		557.3

Biological Activity Assessment

[0555]

Table 2. *In Vitro* ICso data for selected compounds.

Compound no.	PI3K α ICso	PI3K β ICso	PI3K δ ICso	PI3K γ IC_{50}	RAJI p110 δ assay IC_{50}	Raw264.7 p110γ assay IC_{50}	PI3K δ/ PI3KγIC_{50} (selectivity)	RAJI δ/ Raw264.7 γ ICso (selectivity)
2	D2	D2	D2	C3	C4	A5	X	Y
3	D2	D2	D2	D3	D4	B5	W	X
4	C2	C2	D2	A3	B4	A5	Y	Y
5	D2	D2	A2	D3	A4	A5	V	W

(continued)

Compound no.	PI3K α ICso	PI3K β ICso	PI3K δ ICso	PI3K γ IC_{50}	RAJI p110 δ assay IC_{50}	Raw264.7 p110γ assay IC_{50}	PI3K δ/ PI3Kγ IC_{50} (selectivity)	RAJI δ/ Raw264.7 γ ICso (selectivity)
6	D2	D2	D2	B3	C4	A5	Y	X
7	D2	D2	D2	B3	C4	A5	Y	Y
8	D2	D2	D2	C3	D4	C5	X	W
9	C2	C2	C2	B3	B4	A5	X	Y
10	D2	D2	D2	B3	D4	A5	X	X
11	D2	D2	D2	B3	D4	B5	X	X
12	D2	C2	C2	A3	B4	A5	X	X
13	D2	C2	B2	A3	A4	A5	X	W
14	C2	C2	A2	A3	A4	A5	X	W
15	D2	D2	B2	A3	B4	A5	X	W
16	D2	C2	C2	A3	B4	A5	Y	X
17	D2	D2	D2	B3	B4	A5	Y	Y
18	D2	D2	D2	B3	B4	A5	Y	X
19	D2	D2	D2	B3	C4	A5	Y	Y
20	D2	D2	C2	A3	B4	A5	X	X
22	D2	D2	D2	B3	D4	A5	X	X
23	C2	C2	D2	D3	B4	A5	W	W
24	C2	C2	C2	D3	B4	A5	W	W
25	C2	C2	D2	C3	B4	A5	X	X
26	D2	D2	D2	B3	B4	A5	X	Y
27	D2	D2	D2	B3	A4	A5	X	Y
28	D2	D2	D2	D3	B4	A5	W	X
29	D2	C2	C2	B3	A4	A5	X	W
30	D2	D2	D2	B3	B4	A5	Y	Y
31	D2	D2	D2	B3	B4	B5	X	W
32	D2	D2	D2	B3	C4	A5	Y	Y
33	D2	D2	D2	A3	B4	A5	Y	W
34	D2	D2	D2	C3	C4	B5	X	X
35	D2	D2	D2	B3	C4	A5	Y	Y
36	C2	A2	C2	A3	B4	C5	X	W
37	D2	D2	D2	D3	D4	A5	W	Y
38	D2	D2	D2	A3	C4	A5	Y	Y
39	D2	D2	D2	B3	D4	B5	X	X
40	C2	D2	D2	A3	B4	A5	Y	Y
41	D2	D2	D2	B3	B4	A5	Y	Y
42	D2	D2	D2	B3	C4	A5	X	X

(continued)

Compound no.	PI3K α ICso	PI3K β ICso	PI3K δ ICso	PI3K γ IC_{50}	RAJI p110 δ assay IC_{50}	Raw264.7 p110γ assay IC_{50}	PI3K δ/ PI3Kγ IC_{50} (selectivity)	RAJI δ/ Raw264.7 γ ICso (selectivity)
43	D2	D2	D2	B3	B4	A5	Y	X
44	D2	C2	C2	D3	A4	B5	W	V
52	D2	D2	D2	B3	C4	A5	Y	Y
53	D2	D2	D2	D3	C4	B5	W	X
54	C2	C2	C2	A3	B4	A5	Y	W
56	D2	D2	D2	B3	B4	C5	X	V
57	D2	D2	D2	C3	B4	B5	W	W
58	D2	D2	D2	D3	C4	C5	W	V
59	D2	D2	D2	B3	B4	A5	X	X
60	D2	D2	D2	B3	B4	A5	X	Y
61	D2	D2	D2	C3	D4	A5	X	Y
62	D2	D2	D2	C3	D4	C5	X	V
64	D2	D2	D2	D3	D4	C5	W	X
65	D2	D2	D2	D3	D4	C5	W	X
66	D2	C2	C2	A3	B4	A5	X	X
67	D2	D2	D2	D3	D4	C5	W	X
68	D2	D2	D2	D3	D4	C5	W	W
69	D2	D2	D2	D3	ND	C5	W	ND
70	D2	D2	D2	B3	A4	A5	X	X
71	D2	D2	D2	E3	D4	ND	V	ND
72	D2	D2	D2	C3	D4	C5	X	W
73	D2	D2	D2	B3	C4	A5	X	Y
74	D2	D2	C2	C3	D4	C5	W	W
75	D2	D2	D2	D3	D4	A5	W	Y
76	D2	D2	D2	B3	B4	A5	Y	X
77	D2	D2	D2	A3	C4	A5	Y	Y
78	D2	D2	D2	B3	B4	A5	X	X
79	D2	D2	D2	C3	D4	A5	X	Y
80	C2	C2	D2	A3	B4	A5	Y	Y
81	C2	C2	C2	A3	ND	ND	Y	ND
82	D2	D2	D2	B3	C4	A5	X	X
83	D2	D2	D2	C3	C4	A5	X	X
84	D2	D2	D2	A3	B4	A5	Y	X
85	D2	D2	D2	C3	ND	ND	X	ND
86	D2	C2	C2	B3	ND	ND	X	ND
93	D2	D2	D2	A3	ND	ND	Y	ND

(continued)

Compound no.	PI3K α ICso	PI3K β ICso	PI3K δ ICso	PI3K γ IC_{50}	RAJI p110 δ assay IC_{50}	Raw264.7 p110γ assay IC_{50}	PI3K δ/ PI3KγIC_{50} (selectivity)	RAJI δ/ Raw264.7 γ ICso (selectivity)
94	C2	B2	D2	B3	ND	ND	X	ND
95	D2	D2	D2	B3	ND	ND	X	ND
96	C2	D2	D2	A3	ND	ND	Y	ND
97	D2	D2	D2	B3	ND	ND	X	ND
98	D2	D2	D2	B3	ND	ND	X	ND
99	D2	D2	D2	D3	ND	ND	X	ND
100	C2	C2	D2	A3	ND	ND	Y	ND
101	D2	D2	D2	A3	ND	ND	Y	ND
102	D2	D2	D2	B3	ND	ND	X	ND
103	D2	D2	D2	C3	ND	ND	X	ND
104	C2	C2	D2	A3	ND	ND	Y	ND
105	C2	D2	D2	A3	ND	ND	Y	ND
106	D2	C2	D2	A3	ND	ND	Y	ND
107	D2	D2	D2	D3	ND	ND	X	ND
108	D2	D2	D2	B3	ND	ND	X	ND

[0556] The data in Table 2 are coded as follows.

For **PI3K** α, β, and δ IC_{50}:	For PI3K γ IC_{50}:	RAJI p110 δassay IC_{50}	Raw264.7 p110 γ assay IC_{50}
A2 = 1 to <500 nM	A3 = 1 to <100 nM	A4 = 1 to <100 nM	A5 = 1 to <50 nM
B2 = 500 to <1000 nM	B3 = 100 to <500 nM	B4 = 100 to <500 nM	B5 = 50 to <100 nM
C2 = 1000 to <5000 nM	C3 = 500 to <1000 nM	C4 = 500 to <1000 nM	C5 = 100 to <10000 nM
D2 = 5000 to 10000 nM	D3 = 1000 to 5000 nM	D4 = 1000 to 10000 nM	
	E3 = > 5000 nM		
δ/ γ IC_{50} selectivity:	ND = not determined		
V = 0.1 to 1			
W = >1 to <10			
X = 10 to <50			
Y = 50 to <850			

Example 222: PI3-Kinase HTRF™ Assay

[0557] A PI3-Kinase HTRF® assay kit (cat No. 33-016) purchased from Millipore Corporation was used to screen compounds provided herein. This assay used specific, high affinity binding of the GRP1 pleckstrin homology (PH) domain to PIP3, the product of a Class 1A or 1B PI3 Kinase acting on its physiological substrate PIP2. During the detection phase of the assay, a complex was generated between the GST-tagged PH domain and biotinylated short chain PIP3.

The biotinylated PIP3 and the GST-tagged PH domain recruited fluorophores (Streptavidin-Allophycocyanin and Europium-labeled anti-GST respectively) to form the fluorescence resonance energy transfer (FRET) architecture, generating a stable time-resolved FRET signal. The FRET complex was disrupted in a competitive manner by non-biotinylated PIP3, a product formed in the PI3 Kinase assay.

[0558] PI3 Kinase α, β, γ or δ activity was assayed using the PI3 Kinase HTRF® assay kit (catalogue No. 33-016) purchased from Millipore Corporation. Purified recombinant PI3Kα (catalogue No. 14-602-K), PI3Kβ (catalogue No. 14-603-K), PI3Kγ (catalogue No. 14-558-K), and PI3Kδ (catalogue No. 14-604-K) were obtained from Millipore Corporation. Purified recombinant PI3K enzyme was used to catalyze the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2 at 10 μM) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) in the presence of 10 μM ATP. The assay was carried out in 384-well format and detected using a Perkin Elmer EnVision Xcite Multilabel Reader. Emission ratios were converted into percent inhibitions and imported into GraphPad Prism software. The concentration necessary to achieve inhibition of enzyme activity by 50% (IC_{50}) was calculated using concentrations ranging from 20 μM to 0.1 nM (12-point curve). IC_{50} values were determined using a nonlinear regression model available in GraphPad Prism 5.

Example 223: Chemical Stability

[0559] The chemical stability of one or more subject compounds is determined according to standard procedures known in the art. The following details an exemplary procedure for ascertaining chemical stability of a subject compound. The default buffer used for the chemical stability assay is phosphate-buffered saline (PBS) at pH 7.4; other suitable buffers can be used. A subject compound is added from a 100 μM stock solution to an aliquot of PBS (in duplicate) to give a final assay volume of 400 μL, containing 5 μM test compound and 1% DMSO (for half-life determination a total sample volume of 700 μL is prepared). Reactions are incubated, with shaking, for 24 hours at 37 °C; for half-life determination samples are incubated for 0, 2, 4, 6, and 24 hours. Reactions are stopped by adding immediately 100 μL of the incubation mixture to 100 μL of acetonitrile and vortexing for 5 minutes. The samples are then stored at -20 °C until analysis by HPLC-MS/MS. Where desired, a control compound or a reference compound such as chlorambucil (5 μM) is tested simultaneously with a subject compound of interest, as this compound is largely hydrolyzed over the course of 24 hours. Samples are analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 24 hours relative to the amount remaining at time zero, expressed as percent, is reported as chemical stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 224: Expression and Inhibition Assays of p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ:

[0560] Class I PI3-Ks can be either purchased (p110α/p85α, p110p/p85a, p110δ/p85α from Upstate, and p110γ from Sigma) or expressed as previously described (Knight *et al.,* 2004). IC_{50} values are measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions are performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM $MgCl_2$), and freshly sonicated phosphatidylinositol (100 μg/ml). Reactions are initiated by the addition of ATP containing 10 μCi of γ-32P-ATP to a final concentration of 10 or 100 μM and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions are then terminated by the addition of 105 μL IN HCl followed by 160 μL $CHCl_3$:MeOH (1:1). The biphasic mixture is vortexed, briefly centrifuged, and the organic phase is transferred to a new tube using a gel loading pipette tip precoated with $CHCl_3$. This extract is spotted on TLC plates and developed for 3-4 hours in a 65:35 solution of *n*-propanol:1M acetic acid. The TLC plates are then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity is measured at 10-12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 μM). For compounds showing significant activity, IC_{50} determinations are repeated two to four times, and the reported value is the average of these independent measurements.

[0561] Other commercial kits or systems for assaying PI3-K activities are available. The commercially available kits or systems can be used to screen for inhibitors and/or agonists of PI3-Ks including, but not limited to, PI 3-Kinase α, β, δ, and γ. An exemplary system is PI 3-Kinase (human) HTRF™ Assay from Upstate. The assay can be carried out according to the procedures suggested by the manufacturer. Briefly, the assay is a time resolved FRET assay that indirectly measures PIP3 product formed by the activity of a PI3-K. The kinase reaction is performed in a microtiter plate (*e.g.,* a 384 well microliter plate). The total reaction volume is approximately 20 μL per well. In the first step, each well receives 2 μL of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration. Next, approximately 14.5 μL of a kinase/PIP2 mixture (diluted in IX reaction buffer) is added per well for a final concentration of 0.25-0.3 μg/mL kinase and 10 μM PIP2. The plate is sealed and incubated for 15 minutes at room temperature. To start

the reaction, 3.5 μL of ATP (diluted in IX reaction buffer) is added per well for a final concentration of 10 μM ATP. The plate is sealed and incubated for 1 hour at room temperature. The reaction is stopped by adding 5 μL of Stop Solution per well and then 5 μL of Detection Mix is added per well. The plate is sealed, incubated for 1 hour at room temperature, and then read on an appropriate plate reader. Data is analyzed and IC_{50}s are generated using GraphPad Prism 5.

Example 225: B Cell Activation and Proliferation Assay

[0562] The ability of one or more subject compounds to inhibit B cell activation and proliferation is determined according to standard procedures known in the art. For example, an *in vitro* cellular proliferation assay is established that measures the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Balb/c splenic B cells are purified over a Ficoll-Paque™ PLUS gradient followed by magnetic cell separation using a MACS B cell Isolation Kit (Miletenyi). Cells are plated in 90 μL at 50,000 cells/well in B Cell Media (RPMI + 10% FBS + Penn/Strep + 50 μM bME + 5 mM HEPES). A compound provided herein is diluted in B Cell Media and added in a 10 μL volume. Plates are incubated for 30 min at 37 °C and 5% CO_2 (0.2% DMSO final concentration). A 50 μL B cell stimulation cocktail is then added containing either 10 μg/mL LPS or 5 μg/mL F(ab')2 Donkey anti-mouse IgM plus 2 ng/mL recombinant mouse IL4 in B Cell Media. Plates are incubated for 72 hours at 37 °C and 5% CO_2. A volume of 15 μL of Alamar Blue reagent is added to each well and plates are incubated for 5 hours at 37 °C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} or EC_{50} values are calculated using GraphPad Prism 5.

Example 226: Tumor Cell Line Proliferation Assay

[0563] The ability of one or more subject compounds to inhibit tumor cell line proliferation can be determined according to standard procedures known in the art. For instance, an *in vitro* cellular proliferation assay can be performed to measure the metabolic activity of live cells. The assay is performed in a 96-well microtiter plate using Alamar Blue reduction. Human tumor cell lines are obtained from ATCC *(e.g.,* MCF7, U-87 MG, MDA-MB-468, PC-3), grown to confluency in T75 flasks, trypsinized with 0.25% trypsin, washed one time with Tumor Cell Media (DMEM + 10%FBS), and plated in 90 μL at 5,000 cells/well in Tumor Cell Media. A compound provided herein is diluted in Tumor Cell Media and added in a 10 μL volume. Plates are incubated for 72 hours at 37 °C and 5% CO_2. A volume of 10 μL of Alamar Blue reagent is added to each well and plates are incubated for 3 hours at 37 °C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} values are calculated using GraphPad Prism 5.

Example 227: Antitumor Activity *in vivo*

[0564] The compounds described herein can be evaluated in a panel of human and murine tumor models.

Paclitaxel-Refractory Tumor Models

1. Clinically-Derived Ovarian Carcinoma Model.

[0565] This tumor model is established from a tumor biopsy of an ovarian cancer patient. Tumor biopsy is taken from the patient. The compounds described herein are administered to nude mice bearing staged tumors using an every 2 days x 5 schedule.

2. A2780Tax Human Ovarian Carcinoma Xenograft (Mutated Tubulin).

[0566] A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. It is derived from the sensitive parent A2780 line by co-incubation of cells with paclitaxel and verapamil, an MDR-reversal agent. Its resistance mechanism has been shown to be non-MDR related and is attributed to a mutation in the gene encoding the beta-tubulin protein. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

3. HCT116/VM46 Human Colon Carcinoma Xenograft (Multi-Drug Resistant).

[0567] HCT116/VM46 is an MDR-resistant colon carcinoma developed from the sensitive HCT116 parent line. *In vivo,* grown in nude mice, HCT116/VM46 has consistently demonstrated high resistance to paclitaxel. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

4. M5076 Murine Sarcoma Model

[0568] M5076 is a mouse fibrosarcoma that is inherently refractory to paclitaxel *in vivo*. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[0569] One or more compounds as provided herein can be used in combination with other therapeutic agents *in vivo* in the multidrug resistant human colon carcinoma xenografts HCT/VM46 or any other model known in the art including those described herein.

[0570] In one aspect, compounds provided herein may be evaluated in the following models according to methods known in the art. The dosage and schedule of administration may be varied depending on the model. The results may be evaluated with those of selective delta inhibitors, and combinations of delta and gamma inhibitors, and/or with antibodies that block specific inhibitory receptors.

Pancreatic Models

[0571] KPC model is a transgenic mouse model of pancreatic ductal adenocarcinoma (PDA), in which there is conditional expression of both mutant KrasG12D and p53R172H alleles in pancreatic cells. Tumors develop spontaneously in this mouse over a period of 3 -6 months, and can be used to study prophylactic, as well as therapeutic efficacy with novel agents. Cells from these KPC tumors can also be adoptively transferred into syngeneic B6.129 hybrid mice, creating a model with a shorter latency period and allowing large number of animals with tumors to be synchronously established. See e.g., Cancer Cell 7:468 (2005).

[0572] Pan02 model: The murine pancreatic adenocarcinoma cell line Pan02 is a nonmetastatic tumor line, syngeneic to C57BL/6. It can be studied following sc. injection into flank, or orthotopically following injection directly into the pancreas. See e.g., Cancer Res. 44: 717-726 (1984).

Lung Models

[0573] LLC Lewis Lung Adenocarcinoma model: LLC cells are derived from a spontaneous lung tumor from a C57BL/6 mouse and can be studied as a s.c. tumor when injected in the flank, or as an orthotopic tumor if injected i.v., following which it localizes to the lung.

[0574] LLC cells have also been modified to express a peptide from ovalbumin (LL2-OVA cells). Use of these cells, following either s.c. or i.v. injection, allows the tracking of OVA-specific CD8+ lymphocyctes and measurement of effects of therapy on the adaptive immune response against the tumor. See e.g., Science 330:827 (2010).

Breast Model

[0575] The 4T1 mammary carcinoma is a transplantable tumor cell line that grows in syngeneic BALB/c mice. It is highly tumorigenic and invasive and, unlike most tumor models, can spontaneously metastasize from the primary tumor in the mammary gland to multiple distant sites including lymph nodes, blood, liver, lung, brain, and bone. See *e.g.*, Current Protocols in Immunology Unit 20.2 (2000).

Lymphoma Model

[0576] EL4 is a C57BL/6 T thymoma and EG7 is an OVA-expressing subclone of EL4. The parental EL4 line has been modified to constitutively express luciferase, which allows non-invasive imaging of tumor growth throughout the animal using the Xenogen imaging platform.

Melanoma Model

[0577] B16 murine melanoma cells are syngeneic with C57BL/6 mice and can be studied after s.c. or i.v. injection. Placement at either site will result in metastases to lung and other organs. This model has been extensively studied in terms of the role that inhibitory receptors play in the anti-tumor immune response. See e.g., PNAS 107:4275 (2010).

Example 228: Microsome Stability Assay

[0578] The stability of one or more subject compounds is determined according to standard procedures known in the art. For example, stability of one or more subject compounds is established by an *in vitro* assay. For example, an *in vitro* microsome stability assay is established that measures stability of one or more subject compounds when reacting with mouse, rat or human microsomes from liver. The microsome reaction with compounds is performed in 1.5 mL Eppendorf

tube. Each tube contains 0.1 μL of 10.0 mg/mL NADPH; 75 μL of 20.0 mg/mL mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 425 μL of ddH_2O. Negative control (without NADPH) tube contains 75 μL of 20.0 mg/mL mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 525 μL of ddH_2O. The reaction is started by adding 1.0 μL of 10.0 mM tested compound. The reaction tubes are incubated at 37 °C. 100 μL sample is collected into new Eppendorf tube containing 300 μL cold methanol at 0,5, 10, 15, 30 and 60 minutes of reaction. Samples are centrifuged at 15,000 rpm to remove protein. Supernatant of centrifuged sample is transferred to new tube. Concentration of stable compound after reaction with microsome in the supernatant is measured by Liquid Chromatography/Mass Spectrometry (LC-MS).

Example 229: Plasma Stability Assay

[0579] The stability of one or more subject compounds in plasma is determined according to standard procedures known in the art. *See, e.g.,* Rapid Commun. Mass Spectrom., 10: 1019-1026. The following procedure is an HPLC-MS/MS assay using human plasma; other species including monkey, dog, rat, and mouse are also available. Frozen, heparinized human plasma is thawed in a cold water bath and spun for 10 minutes at 2000 rpm at 4 °C prior to use. A subject compound is added from a 400 μM stock solution to an aliquot of pre-warmed plasma to give a final assay volume of 400 μL (or 800 μL for half-life determination), containing 5 μM test compound and 0.5 % DMSO. Reactions are incubated, with shaking, for 0 minutes and 60 minutes at 37 C, or for 0, 15, 30, 45 and 60 minutes at 37 C for half life determination. Reactions are stopped by transferring 50 μL of the incubation mixture to 200 μL of ice-cold acetonitrile and mixed by shaking for 5 minutes. The samples are centrifuged at 6000 x g for 15 minutes at 4 °C and 120 μL of supernatant removed into clean tubes. The samples are then evaporated to dryness and submitted for analysis by HPLC-MS/MS.

[0580] In one embodiment, one or more control or reference compounds (5 μM) are tested simultaneously with the test compounds: one compound, propoxycaine, with low plasma stability and another compound, propantheline, with intermediate plasma stability.

[0581] Samples are reconstituted in acetonitrile/methanol/water (1/1/2, v/v/v) and analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 60 minutes relative to the amount remaining at time zero, expressed as percent, is reported as plasma stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 230: Kinase Signaling in Blood

[0582] PI3K/Akt/mTOR signaling is measured in blood cells using the phosflow method (Methods Enzymol. (2007) 434:131-54). This method is by nature a single cell assay so that cellular heterogeneity can be detected rather than population averages. This allows concurrent distinction of signaling states in different populations defined by other markers. Phosflow is also highly quantitative. To test the effects of one or more compounds provided herein, unfractionated splenocytes, or peripheral blood mononuclear cells are stimulated with anti-CD3 to initiate T-cell receptor signaling. The cells are then fixed and stained for surface markers and intracellular phosphoproteins. Inhibitors provided herein inhibit anti-CD3 mediated phosphorylation of Akt -S473 and S6, whereas rapamycin inhibits S6 phosphorylation and enhances Akt phosphorylation under the conditions tested.

[0583] Similarly, aliquots of whole blood are incubated for 15 minutes with vehicle (e.g., 0.1% DMSO) or kinase inhibitors at various concentrations, before addition of stimuli to crosslink the T cell receptor (TCR) (anti-CD3 with secondary antibody) or the B cell receptor (BCR) using anti-kappa light chain antibody (Fab'2 fragments). After approximately 5 and 15 minutes, samples are fixed (e.g., with cold 4% paraformaldehyde) and used for phosflow. Surface staining is used to distinguish T and B cells using antibodies directed to cell surface markers that are known to the art. The level of phosphorylation of kinase substrates such as Akt and S6 are then measured by incubating the fixed cells with labeled antibodies specific to the phosphorylated isoforms of these proteins. The population of cells are then analyzed by flow cytometry.

Example 231: Colony Formation Assay

[0584] Murine bone marrow cells freshly transformed with a p190 BCR-Abl retrovirus (herein referred to as p190 transduced cells) are plated in the presence of various drug combinations in M3630 methylcellulose media for about 7 days with recombinant human IL-7 in about 30% serum, and the number of colonies formed is counted by visual examination under a microscope.

[0585] Alternatively, human peripheral blood mononuclear cells are obtained from Philadelphia chromosome positive (Ph+) and negative (Ph-) patients upon initial diagnosis or relapse. Live cells are isolated and enriched for CD19+ CD34+ B cell progenitors. After overnight liquid culture, cells are plated in methocult GF+ H4435 (Stem Cell Technologies), supplemented with cytokines (IL-3, IL-6, IL-7, G-CSF, GM-CSF, CF, Flt3 ligand, and erythropoietin) and various concentrations of known chemotherapeutic agents in combination with compounds of the present disclosure. Colonies are counted by microscopy 12-14 days later. This method can be used to test for evidence of additive or synergistic activity.

Example 232: *In Vivo* Effect of Kinase Inhibitors on Leukemic Cells

[0586] Female recipient mice are lethally irradiated from a γ source in two doses about 4 hr apart, with approximately 5Gy each. About 1 hr after the second radiation dose, mice are injected i.v. with about 1x 10^6 leukemic cells *(e.g.,* Ph+ human or murine cells, or p190 transduced bone marrow cells). These cells are administered together with a radioprotective dose of about 5x 10^6 normal bone marrow cells from 3-5 week old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs are harvested for analysis. Kinase inhibitor treatment begins about 10 days after leukemic cell injection and continues daily until the mice become sick or a maximum of approximately 35 days post-transplant. Inhibitors are given by oral lavage.

[0587] Peripheral blood cells are collected approximately on day 10 (pre-treatment) and upon euthanization (post treatment), contacted with labeled anti-hCD4 antibodies and counted by flow cytometry. This method can be used to demonstrate that the synergistic effect of one or more compounds provided herein in combination with known chemotherapeutic agents can reduce leukemic blood cell counts as compared to treatment with known chemotherapeutic agents (e.g., Gleevec) alone under the conditions tested.

Example 233: Treatment of Lupus Disease Model Mice

[0588] Mice lacking the inhibitory receptor FcγRIIb that opposes PI3K signaling in B cells develop lupus with high penetrance. FcγRIIb knockout mice (R2KO, Jackson Labs) are considered a valid model of the human disease as some lupus patients show decreased expression or function of FcγRIIb (S. Bolland and J.V. Ravtech 2000. Immunity 12:277-285).

[0589] The R2KO mice develop lupus-like disease with anti-nuclear antibodies, glomerulonephritis and proteinurea within about 4-6 months of age. For these experiments, the rapamycin analogue RAD001 (available from LC Laboratories) is used as a benchmark compound, and administered orally. This compound has been shown to ameliorate lupus symptoms in the B6.Slelz.Sle3z model (T. Wu et al. J. Clin Invest. 117:2186-2196).

[0590] The NZB/W F1 mice that spontaneously develop a systemic autoimmune disease is a model of lupus. The mice are treated starting at 20 weeks of age for a profilactic model and at 23 weeks of age for a therapeutic model. Blood and urine samples are obtained throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA. Glomerulonephritis is assessed in kidney sections stained with H&E at the end of the study, or survival can be an endpoint. For example, the proteozome inhibitor Bortezimib is effective at blocking disease in the NZB/W model in both the profilactic and therapeutic model with reductions in auto-antibody production, kidney damage, and improvements in survival *(*Nature Medicine 14, 748-755 (2008)).

[0591] Lupus disease model mice such as R2KO, BXSB or MLR/lpr are treated at about 2 months old, approximately for about two months. Mice are given doses of: vehicle, RAD001 at about 10 mg/kg, or compounds provided herein at approximately 1 mg/kg to about 500 mg/kg. Blood and urine samples are obtained throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA. Animals are euthanized at day 60 and tissues harvested for measuring spleen weight and kidney disease. Glomerulonephritis is assessed in kidney sections stained with H&E. Other animals are studied for about two months after cessation of treatment, using the same endpoints.

[0592] This established art model can be employed to demonstrate that the kinase inhibitors provided herein can suppress or delay the onset of lupus symptoms in lupus disease model mice.

Example 234: Murine Bone Marrow Transplant Assay

[0593] Female recipient mice are lethally irradiated from a γ ray source. About 1 hr after the radiation dose, mice are injected with about 1x106 leukemic cells from early passage p190 transduced cultures *(e.g.,* as described in Cancer Genet Cytogenet. 2005 Aug; 161(1):51-6). These cells are administered together with a radioprotective dose of approximately 5x 10^6 normal bone marrow cells from 3-5 wk old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs harvested for flow cytometry and/or magnetic enrichment. Treatment begins on approximately day 10 and continues daily until mice become

sick, or after a maximum of about 35 days post-transplant. Drugs are given by oral gavage (p.o.). In a pilot experiment, a dose of chemotherapeutic that is not curative but delays leukemia onset by about one week or less is identified; controls are vehicle-treated or treated with chemotherapeutic agent, previously shown to delay but not cure leukemogenesis in this model (e.g., imatinib at about 70 mg/kg twice daily). For the first phase, p190 cells that express eGFP are used, and postmortem analysis is limited to enumeration of the percentage of leukemic cells in bone marrow, spleen and lymph node (LN) by flow cytometry. In the second phase, p190 cells that express a tailless form of human CD4 are used and the postmortem analysis includes magnetic sorting of hCD4+ cells from spleen followed by immunoblot analysis of key signaling endpoints: p Akt -T308 and S473; pS6 and p4EBP-1. As controls for immunoblot detection, sorted cells are incubated in the presence or absence of kinase inhibitors of the present disclosure inhibitors before lysis. Optionally, "phosflow" is used to detect p Akt -S473 and pS6-S235/236 in hCD4-gated cells without prior sorting. These signaling studies are particularly useful if, for example, drug-treated mice have not developed clinical leukemia at the 35 day time point. Kaplan-Meier plots of survival are generated and statistical analysis done according to methods known in the art. Results from p190 cells are analyzed separated as well as cumulatively.

[0594] Samples of peripheral blood (100-200 μL) are obtained weekly from all mice, starting on day 10 immediately prior to commencing treatment. Plasma is used for measuring drug concentrations, and cells are analyzed for leukemia markers (eGFP or hCD4) and signaling biomarkers as described herein.

[0595] This general assay known in the art can be used to demonstrate that effective therapeutic doses of the compounds provided herein can be used for inhibiting the proliferation of leukemic cells.

Example 235: Matrigel Plug Angiogenesis Assay

[0596] Matrigel containing test compounds are injected subcutaneously or intraocularly, where it solidifies to form a plug. The plug is recovered after 7-21 days in the animal and examined histologically to determine the extent to which blood vessels have entered it. Angiogenesis is measured by quantification of the vessels in histologic sections. Alternatively, fluorescence measurement of plasma volume is performed using fluorescein isothiocyanate (FITC)-labeled dextran 150. The results are expected to indicate one or more compounds provided herein that inhibit angiogenesis and are thus expected to be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 236: Corneal Angiogenesis Assay

[0597] A pocket is made in the cornea, and a plug containing an angiogenesis inducing formulation (e.g., VEGF, FGF, or tumor cells), when introduced into this pocket, elicits the ingrowth of new vessels from the peripheral limbal vasculature. Slow-release materials such as EL VAX (ethylene vinyl copolymer) or Hydron are used to introduce angiogenesis inducing substances into the corneal pocket. Alternatively, a sponge material is used.

[0598] The effect of putative inhibitors on the locally induced (e.g., sponge implant) angiogenic reaction in the cornea *(e.g.,* by FGF, VEGF, or tumor cells). The test compound is administered orally, systemically, or directly to the eye. Systemic administration is by bolus injection or, more effectively, by use of a sustained- release method such as implantation of osmotic pumps loaded with the test inhibitor. Administration to the eye is by any of the methods described herein including, but not limited to eye drops, topical administration of a cream, emulsion, or gel, intravitreal injection.

[0599] The vascular response is monitored by direct observation throughout the course of the experiment using a stereomicroscope in mice. Definitive visualization of the corneal vasculature is achieved by administration of fluorochrome-labeled high-molecular weight dextran. Quantification is performed by measuring the area of vessel penetration, the progress of vessels toward the angiogenic stimulus over time, or in the case of fluorescence, histogram analysis or pixel counts above a specific (background) threshold.

[0600] The results can indicate one or more compounds provided herein inhibit angiogenesis and thus can be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 237: Microtiter-plate Angiogenesis Assay

[0601] The assay plate is prepared by placing a collagen plug in the bottom of each well with 5-10 cell spheroids per collagen plug each spheroid containing 400-500 cells. Each collagen plug is covered with 1100 μL of storage medium per well and stored for future use (1-3 days at 37 °C, 5% CO_2). The plate is sealed with sealing. Test compounds are dissolved in 200 μL assay medium with at least one well including a VEGF positive control and at least one well without VEGF or test compound as a negative control. The assay plate is removed from the incubator and storage medium is carefully pipeted away. Assay medium containing the test compounds are pipeted onto the collagen plug. The plug is placed in a humidified incubator for (37 °C, 5% CO_2) 24-48 hours. Angiogenesis is quantified by counting the number of sprouts, measuring average sprout length, or determining cumulative sprout length. The assay can be preserved for later analysis by removing the assay medium, adding 1 mL of 10% paraformaldehyde in Hanks BSS per well, and storing

at 4 °C. The results are expected to identify compounds that inhibit angiogenesis in various cell types tested, including cells of ocular origin.

Example 238: Combination Use of PI3K-δ Inhibitors and Agents that Inhibit IgE Production or Activity

[0602] The compounds as provided herein can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Agents that inhibit IgE production include, for example, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs *(i.e.,* rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as Omalizumab and TNX-901.

[0603] One or more of the subject compounds capable of inhibiting PI3K-δ can be efficacious in treatment of autoimmune and inflammatory disorders (AIID), for example, rheumatoid arthritis. If any of the compounds causes an undesired level of IgE production, one can choose to administer it in combination with an agent that inhibits IgE production or IgE activity. Additionally, the administration of PI3K-δ or PI3K-δ/γ inhibitors as provided herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway. Various *in vivo* and *in vitro* models can be used to establish the effect of such combination treatment on AIID including, but not limited to: (a) *in vitro* B-cell antibody production assay, (b) *in vivo* TNP assay, and (c) rodent collagen induced arthritis model.

(a) B-cell Assay

[0604] Mice are euthanized, and the spleens are removed and dispersed through a nylon mesh to generate a single-cell suspension. The splenocytes are washed (following removal of erythrocytes by osmotic shock) and incubated with anti-CD43 and anti-Mac-1 antibody-conjugated microbeads (Miltenyi Biotec). The bead-bound cells are separated from unbound cells using a magnetic cell sorter. The magnetized column retains the unwanted cells and the resting B cells are collected in the flow-through. Purified B-cells are stimulated with lipopolysaccharide or an anti-CD40 antibody and interleukin 4. Stimulated B-cells are treated with vehicle alone or with PI3K-δ inhibitors as provided herein with and without mTOR inhibitors such as rapamycin, rapalogs, or mTORC1/C2 inhibitors. The results are expected to show that in the presence of mTOR inhibitors (*e.g.*, rapamycin) alone, there is little to no substantial effect on IgG and IgE response. However, in the presence of PI3K-δ and mTOR inhibitors, the B-cells are expected to exhibit a decreased IgG response as compared to the B-cells treated with vehicle alone, and the B-cells are expected to exhibit a decreased IgE response as compared to the response from B-cells treated with PI3K-δ inhibitors alone.

(b) TNP Assay

[0605] Mice are immunized with TNP-Ficoll or TNP-KHL and treated with: vehicle, a PI3K-δ inhibitor, an mTOR inhibitor, for example rapamycin, or a PI3K-δ inhibitor in combination with an mTOR inhibitor such as rapamycin. Antigen-specific serum IgE is measured by ELISA using TNP-BSA coated plates and isotype specific labeled antibodies. It is expected that mice treated with an mTOR inhibitor alone exhibit little or no substantial effect on antigen specific IgG3 response and no statistically significant elevation in IgE response as compared to the vehicle control. It is also expected that mice treated with both PI3K-δ inhibitor and mTOR inhibitor exhibit a reduction in antigen specific IgG3 response as compared to the mice treated with vehicle alone. Additionally, the mice treated with both PI3K-δ inhibitor and mTOR inhibitor exhibit a decrease in IgE response as compared to the mice treated with PI3K-δ inhibitor alone.

(c) Rat Collagen Induced Arthritis Model

[0606] Female Lewis rats are anesthetized and given collagen injections prepared and administered as described previously on day 0. On day 6, animals are anesthetized and given a second collagen injection. Caliper measurements of normal (pre-disease) right and left ankle joints are performed on day 9. On days 10-11, arthritis typically occurs and rats are randomized into treatment groups Randomization is performed after ankle joint swelling is obviously established and there is good evidence of bilateral disease.

[0607] After an animal is selected for enrollment in the study, treatment is initiated. Animals are given vehicle, PI3K-δ inhibitor, or PI3K-δ inhibitor in combination with rapamycin. Dosing is administered on days 1-6. Rats are weighed on days 1-7 following establishment of arthritis and caliper measurements of ankles taken every day. Final body weights are taken on day 7 and animals are euthanized.

[0608] The combination treatment using a compound as provided herein and rapamycin can provide greater efficacy than treatment with PI3K-δ inhibitor alone.

Example 239: Delayed Type Hypersensitivity Model

[0609] DTH is induced by sensitizing 60 BALB/c male mice on day 0 and day 1 with a solution of 0.05% 2,4 dinitrofluorobenzene (DNFB) in a 4:1 acetone/olive oil mixture. Mice are gently restrained while 20 μL of solution is applied to the hind foot pads of each mouse. The hind foot pads of the mice are used as they represent an anatomical site that can be easily isolated and immobilized without anesthesia. On day 5, mice are administered a single dose of vehicle, a compound provided herein at 10, 3, 1, or 0.3 mg/kg, or dexamethasone at a dose of 5 mg/kg by oral gavage. Thirty minutes later mice are anaesthetized, and a solution of 0.25% DNFB in a 4:1 acetone/olive oil solution is applied to the left inner and outer ear surface. This application results in the induction of swelling to the left ear and under these conditions, all animals responded to this treatment with ear swelling. A vehicle control solution of 4:1 acetone/olive oil is applied to the right inner and outer ear. Twenty four hours later, mice are anaesthetized, and measurements of the left and right ear are taken using a digital micrometer. The difference between the two ears is recorded as the amount of swelling induced by the challenge of DNFB. Drug treatment groups are compared to vehicle control to generate the percent reduction in ear swelling. Dexamethasone is routinely used as a positive control as it has broad anti-inflammatory activity.

Example 240: Peptidoglycan-Polysaccharide rat Arthritic Model

(a) Systemic arthritis model

[0610] All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O_2 and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intraperitoneally (i.p.) with a single injection of purified PG-PS 10S Group A, D58 strain (concentration 25 μg/g of bodyweight) suspended in sterile 0.85% saline. Each animal receives a total volume of 500 microliters administered in the lower left quadrant of the abdomen using a 1 milliliter syringe with a 23 gauge needle. Placement of the needle is critical to avoid injecting the PG-PS 10S into either the stomach or caecum. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. An acute response of a sharp increase in ankle measurement, typically 20% above baseline measurement can peak in 3-5 days post injection. Treatment with test compounds can be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 30. The animals are weighed on days 0, 1, 2, 3, 4, 5, 6, 7 and beginning again on day 12-30 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, 6 and 7. On day 12, measurements begin again and continue on through day 30. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels, clinical chemistry or hematology parameters. Animals are then euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

(b) Monoarticular arthritis model

[0611] All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O_2 and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intra-articular (i.a.) with a single injection of purified PG-PS 100P Group A, D58 strain (concentration 500 μg/mL) suspended in sterile 0.85% saline. Each rat receives a total volume of 10 microliters administered into the tibiotalarjoint space using a 1 milliliter syringe with a 27 gauge needle. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. Animals that respond 2-3 days later with a sharp increase in ankle measurement, typically 20% above baseline measurement on the initial i.a. injection, are included in the study. On day 14, all responders are anesthetized again using the procedure previously described. Animals receive an intravenous (I.V.) injection of PG-PS (concentration 250 μL/mL). Each rat receives a total volume of 400 microliters administered slowly into the lateral tail vein using a 1 milliliter syringe with a 27 gauge needle. Baseline ankle measurements are measured prior to IV injection and continue through the course of inflammation or out to day 10. Treatment with test compounds will be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 24. The animals are weighed on days 0, 1, 2, 3, 4, 5, and beginning again on day 14-24 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, and beginning again on day 14-24 or until the study is terminated. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels,

clinical chemistry or hematology parameters. Animals are them euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

Example 241: Mice Models for Asthma

[0612] Efficacy of a compound provided herein in treating, preventing and/or managing asthma can be assessed using an conventional animal models including various mice models described in, for example, Nials et al., Dis Model Mech. 1(4-5): 213-220 (2008).

(a) Acute Allergen Challenge Models

[0613] Several models are known in the art and any of such models can be used. Although various allergens can be used to induce asthma-like conditions, the principle is consistent throughout the methods. Briefly, asthma-like conditions are induced through multiple systemic administration of the allergen *(e.g.,* ova, house dust mite extracts and cockroach extracts) in the presence of an adjuvant such as aluminum hydroxide. Alternatively, an adjuvant-free system can be used, but it usually requires a higher number of exposures to achieve suitable sensitization. Once induced, animals exhibit many key features of clinical asthma such as: elevated levels of IgE; airway inflammation; goblet cell hyperplasia; epithelial hypertrophy; AHR ro specific stimuli; and early and late phase bronchoconstriction. Potential efficacy of a compound thus can be assessed by determining whether one or more of these clinical features are reversed or mitigated.

(b) Chronic Allergen Challenge Models

[0614] Chronic allergen challenge models aim to reproduce more of the features of the clinical asthma, such as airway remodeling and persistent AHR, than acute challenge models. While allergens similar to those used in acute allergen challenge models can be used, in chronic allergen challenge models, animals are subjected to repeated exposure of the airways to low levels of allergen for a period of up to 12 weeks. Once induced, animals exhibit key features of human asthma such as: allergen-dependent sensitization; a Th2-dependent allergic inflammation characterized by eosinophillic influx into the airway mucosa; AHR; and airway remodeling as evidenced by goblet cell hyperplasia, epithelial hypertrophy, subepithelial or peribronchiolar fibrosis. Potential efficacy of a compound thus can be assessed by determining whether one or more of these clinical features are reversed or mitigated.

Example 242: Models for Psoriasis

[0615] Efficacy of a compound provided herein in treating, preventing and/or managing psoriasis can be assessed using an conventional animal models including various animal models described in, for example, Boehncke et al., Clinics in Dermatology, 25: 596-605 (2007).

[0616] As an example, the mouse model based on adoptive transfer of $CD4^+CD45RB^{hi}$ T cells described in Hong et al., J Immunol., 162: 7480-7491 (1999) can be made. Briefly, female BALB/cBY (donor) and C.B.-17/Prkdc scid/scid (recipient) mice are housed in a specific pathogen-free environment and are used between 6 and 8 weeks of age. $CD4^+$ T cells are enriched from BALB/cBy splenocytes using a mouse CD4 enrichment kit. The cells are then labeled with PE-conjugated anti-CD4, FITC-conjugated anti-CD45RB, and APC-conjugated anti-CD25 antibodies. Cells are sorted using a cell sorter. $CD4^+CD45RB^{hi}CD25$ cells are collected. Cells are resuspended in saline and $4x\ 10^8$ cells/mouse are injected i.p. into C.B.-17/Prkdc scid/scid mice. Mice may be dosed with LPS, cytokines, or antibodies as necessary. Mice are monitored for external signs of skin lesions twice each week. After the termination, ear, back skin, lymph nodes and spleen may be collected for further *ex vivo* studies.

Example 243: Models for Scleroderma

[0617] A compound's efficacy in treating scleroderma can be tested using animal models. An exemplary animal model is a mouse model for scleroderma induced by repeated local injections of bleomycin ("BLM") described, for example, in Yamamoto et al., J Invest Dermatol 112: 456-462 (1999). This mouse model provides dermal sclerosis that closely resembles systemic sclerosis both histologically and biochemically. The sclerotic changes observed in the model include, but are not limited to: thickened and homogenous collagen bundles and cellular filtrates; gradual increase in number of mast cells; degranulation of mast cells; elevated histamine release; increase in hydroxyproline in skin; presence of anti-nuclear antibody in serum; and strong expression of transforming growth factor β-2 mRNA. Therefore, efficacy of a compound in treating scleroderma can be assessed by monitoring the lessening of one or more of these changes.

[0618] Briefly, the following exemplary procedures can be used to generate the mouse model for scleroderma: Specific pathogen-free, female BALB/C mice and C3H mice of 6 weeks old, weighing about 20 g, are purchased and maintained

with food and water ad libitum. BLM is dissolved in PBS at differing concentrations and sterilized with filtration. Aliquots of each concentration of BLM or PBS are injected subcutaneously into the shaved back of the mice daily for 1-4 weeks with a needle. Alternatively, mice are injected every other day.

[0619] Histolopathological and biochemical changes induced can be assessed using any methods commonly practiced in the field. For example, histopathological changes can be assessed using a standard avidine-biotin peroxidase technique with anti-L3T4 monoclonal antibody, anti-Lyt2 monoclonal antibody, anti-mouse pan-tissue-fixed macrophage antibody, anti-stem cell factor monoclonal antibody, anti-transforming growth factor-β polyclonal antibody, and anti-decorin antibody. Cytokine expression of cellular infiltrates can be assessed by using several anti-cytokine antibodies. Hydroxyproline level can be assessed by hydrolyzing skin pieces with hydrochloric acid, neutralizing with sodium hydroxide, and colorimetrically assessing the hydrolates at 560 nm with p-dimethylaminobenzaldehyde. Pepsin-resistant collagen can be assessed by treating collagen sample extracted from biopsied tissues and analyzing by polyacrylamide stacking gel electrophoresis. Mast cells can be identified by toluidine blue, and cells containing matachromatic granules can be counted under high magnification of a light microscope. Serum levels of various cytokines can be assessed by enzyme-linked immunosorbent assay, and mRNA levels of the cytokines can be assessed by reverse-transcriptase polymerase chain reaction. Autoantibodies in serum can be detected using 3T3 fibroblasts as the substrate for the screening.

Example 244: Models for Myositis

[0620] A compound's efficacy in treating myositis (e.g., dermatomyositis) can be tested using animal models known in the art. One such example is the familial canine dermatomyositis model described in Hargis et al., AJP 120(2): 323-325 (1985). Another example is the rabbit myosin induced mouse model described in Phyanagi et al., Arthritis & Rheumatism, 60(10): 3118-3127 (2009).

[0621] Briefly, 5-week old male SJL/J mice are used. Purified myosin from rabbit skeletal muscle (6.6 mg/ml) is emulsified with an equal amount of Freund's complete adjuvant and 3.3 mg/ml *Mycobacterium butyricum*. The mice are immunized repeatedly with emulsified rabbit myosin. Once myositis is induced, inflammatory cell filtration and necrotic muscle fiber should be evident in the model. In the muscles of animals, $CD4^+$ T cells are mainly located in the perimysum and $CD8^+$ T cells are mainly located in the endomysium and surround non-necrotic muscle fibers. TNFα, IFNγ and perforin are up-regulated and intercellular adhesion molecule 1 is increased in the muscles.

[0622] To assess the efficacy of a compound, following administration of the compound through adequate route at specified dose, the mice are killed and muscle tissues are harvested. The muscle tissue is immediately frozen in chilled isopentane precooled in liquid nitrogen, and then cryostat sections are prepared. The sections are stained with hematoxylin and eosin for counting of number of infiltrated cells. Three sections from each mouse are prepared and photomicrographs are obtained. For immunohistochemical tests, cryostat sections of muscle are dried and fixed in cold acetone at -20 °C. The slides are rehydrated in PBS, and then endogeneous peroxide activity is blocked by incubation in 1% hydrogen peroxide. The sections are incubated overnight with rat anti-mouse CD4 monoclonal antibody, rat anti-mouse CD8 monoclonal antibody, rat anti-mouse F4/80 monoclonal antibody or normal rat IgG in antibody diluent. The samples are washed with PBS and incubated with biotin-conjugated rabbit anti-rat IgG pretreated with 5% normal mouse serum. After washing with PBS, the samples are incubated with streptavidin-horseradish peroxidase. After washing PBS, diaminobenzidine is used for visualization.

Example 245: Models for Sjögren Syndrome

[0623] A compound's efficacy in treating Sjögren's syndrome can be tested using animal models known in the art, for example, those described in Chiorini et al., Journal of Autoimmunity 33: 190-196 (2009). Examples include: mouse model spontaneously developed in first filial generation of NZB mice crossed to NZW mice *(see, e.g.,* Jonsson et al., Clin Immunol Immunopathol 42: 93-101 (1987); mouse model induced by i.p. injection of incomplete Freund's adjuvant *(id.;* Deshmukh et al., J Oral Pathol Med 38: 42-27 (2009)); NOD mouse models wherein Sjögren's phenotype is developed by specific genotypes *(see, e.g.,* Cha et al., Arthritis Rheum 46: 1390-1398 (2002); Kong et al., Clin Exp Rheumatol 16: 675-681 (1998); Podolin et al., J Exp Med 178: 793-803 (1993); and Rasooly et al., Clin Immunol Immunopathol 81: 287-292 (1996)); mouse model developed in spontaneous lpr mutation; mouse model developed in Id3 knock-out mice *(see, e.g.,* Li et al., Immunity 21: 551-560 (2004)); mouse model developed in PI3K knock-out mice (*see, e.g.,* Oak et al., Proc Natl Acad Sci USA 103: 16882-16887 (2006)); mouse model developed in BAFF over-expressing transgenic mice *(see, e.g.,* Groom et al., J Clin Invest 109: 59-68 (2002)); mouse model induced by injection of Ro antigen into BALB/c mice *(see, e.g.,* Oh-Hora et al., Nat. Immunol 9: 432-443 (2008)); mouse model induced by injection of carbonic anhydrase II *(see, e.g.,* Nishimori et al., J Immunol 154: 4865-4873 (1995); mouse model developed in IL-14 over-expressing transgenic mice *(see, e.g.,* Shen et al., J Immunol 177: 5676-5686 (2006)); and mouse model developed in IL-12 expressing transgenic mice *(see, e.g.,* McGrath-Morrow et al., Am J Physiol Lung Cell MolPhysiol 291: L837-846

(2006)).

Example 246: Models for Immune Complex Mediated Disease

[0624] The Arthus reaction is a type 3 immune response to immune complexes, and thus, can be a mechanistic model supporting therapeutic hypothesis for immune complex mediated diseases such as rheumatoid arthritis, lupus and other autoimmune diseases. For example, PI3Kγ and δ deficient mice can be used as experimental models of the Arthus reaction and provide assessment of therapeutic potential of a compound as to the treatment of immune complex mediated diseases. The Arthus reaction can be induced using the following exemplary procedures as described in Konrad et al., Journal of Biological Chemistry (2008 283(48): 33296-33303.

[0625] PI3Kγ- and PI3Kδ-deficient mice are maintained under dry barrier conditions. Mice are anesthetized with ketamine and xylazine, and the trachea is cannulated. Appropriate amount of protein G-purified anti-OVA IgG Ab is applied, and appropriate amount of OVA antigen is given intravenously. For PI3K blocking experiments, wortmanin is given intratracheally together with the application of anti-OVA igG. Mice are killed at 2-4 hours after initiation of inflammation, and desired follow up assessments can be performed using methods known in the art.

Example 247: PI3-Kinase Promega™ Assay

[0626] Promega ADP-Glo Max assay kit (Cat. No. V7002) was utilized to determine IC_{50} values for α, β, δ and γ isoforms of human Class I PI3 kinases (Millipore). Samples of kinase (20 nM α or δ, 40 nM β or γ isoform) were incubated with compound for 15 minutes at room temperature in reaction buffer (15 mM HEPES pH 7.4, 20 mM NaCl, 1 mM EGTA, 0.02% Tween 20, 10 mM $MgCl_2$, 0.2 mg/mL bovine-γ-globulins) followed by addition of ATP/diC8-PtdInsP mixture to give final concentrations of 3 mM ATP and 500 uM diC_8-PtdInsP. Reactions were incubated at room temperature for 2 hours followed by addition of 25 uL of stop solution. After a 40-minute incubation at room temperature, 50 uL of Promega detection mix was added followed by incubation for 1 hour at room temperature. Plates were then read on Envision plate reader in luminescence mode. Data was converted to % inhibition using the following equation below:

$$\%inhibition = 100 - \left(\left[\frac{S - Pos}{Neg - Pos} \right] * 100 \right)$$

where S is the sample luminescence, *Pos* is a positive control without added PI3K, *Neg* is the negative control without added compound. Data was then plotted as % inhibition vs compound concentration. Data fit to 4 parameter logistic equation to determine IC_{50} values:

$$\% \, Inhibition = \frac{\max - \min}{1 - \left(\frac{IC_{50}{}^{h}}{[I]^{h}} \right)}$$

[0627] Certain compounds provided herein were tested in PI3-Kinase Promega Assay using procedures as described above to determine IC_{50} values for α, β, δ and/or γ isoforms. The IC_{50} values are summarized in Table 2.

Example 248: Isoform-Selective Cellular Assays

(a) PI3K-δ Selective Assay

[0628] A compound's ability in selectively inhibiting PI3K-δ can be assessed using RAJI cells, *i.e.,* B lymphocyte cells derived from lymphoma patients. Briefly, serum-starved RAJI cells are stimulated with anti-human IgM, thereby causing signaling through the B-cell receptors, as described in, for example, He et al., Leukemia Research (2009) 33: 798-802. B-cell receptor signaling is important for the activation, differentiation, and survival of B cells and certain B-cell derived cancers. Reduction of phospho-AKT is indicative of compounds that may inhibit B-cell proliferation and function in certain diseases. By monitoring the reduction of phospho-AKT in stimulated RAJI cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kδ can be assessed.

[0629] Certain compounds provided herein were tested in RAJI cell model using procedures as described above. The IC_{50} values for phospho-AKT are summarized in Table 2.

(b) PI3K-γ Selective Assay

[0630] A compound's ability in selectively inhibiting PI3K-γ can be assessed using RAW264.7 macrophages. Briefly, serum-starved RAW264.7 cells are stimulated with a known GPCR agonist C5a. *See, e.g.,* Camps et al., Nature Medicine (2005) 11(9):936-943. Cells can be treated with test compounds prior to, simultaneously with, or subsequent to the stimulation by C5a. RAW 264.7 cells respond to the complement component fragment C5a through activation of the C5a receptor, and the C5a receptor activates macrophages and induces cell migration. Test compounds' ability to inhibit C5a-mediated AKT phosphorylation is indicative of selective inhibition of PI3K-y. Thus, by monitoring the reduction of phospho-AKT in stimulated RAW 264.7 cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kγ can be assessed.

[0631] Certain compounds provided herein were tested in RAW 264.7 cell model using procedures as described above. The IC_{50} values for phospho-AKT are summarized in Table 2.

(c) PI3K-α Selective Assay

[0632] A compound's ability in selectively inhibiting PI3K-α can be assessed using SKOV-3 cells, *i.e.,* human ovarian carcinoma cell line. Briefly, SKOV-3 cells, in which mutant PI3Kα is constitutively active, can be treated with test compounds. Test compounds' ability to inhibit AKT phosphorylation in SKOV-3 cells, therefore, is indicative of selective inhibition of PI3Kα. Thus, by monitoring the reduction of phospho-AKT in SKOV-3 cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kα can be assessed.

(d) PI3K-β Selective Assay

[0633] A compound's ability in selectively inhibiting PI3K-β can be assessed using 786-O cells, *i.e.,* human kidney carcinoma cell line. Briefly, 786-O cells, in which PI3Kβ is constitutively active, can be treated with test compounds. Test compounds' ability to inhibit AKT phosphorylation in 786-O cells, therefore, is indicative of selective inhibition of PI3Kβ. Thus, by monitoring the reduction of phospho-AKT in 786-O cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kβ can be assessed.

[0634] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 2013029982 A1 **[0006]**
- US 2013053362 A1 **[0006]**
- WO 2013154878 A1 **[0006]**
- EP 3119397 A1 **[0006]**
- WO 2013012918 A1 **[0006]**
- WO 2012037204 A1 **[0006]**
- US 5023252 A **[0229]**
- US 4992445 A **[0229]**
- US 5001139 A **[0229]**
- US 4886499 A **[0230]**
- US 5190521 A **[0230]**
- US 5328483 A **[0230]**
- US 5527288 A **[0230]**
- US 4270537 A **[0230]**
- US 5015235 A **[0230]**
- US 5141496 A **[0230]**
- US 5417662 A **[0230]**
- WO 9934850 A **[0230]**
- US 5480381 A **[0230]**
- US 5599302 A **[0230]**
- US 5334144 A **[0230]**
- US 5993412 A **[0230]**
- US 5649912 A **[0230]**
- US 5569189 A **[0230]**
- US 5704911 A **[0230]**
- US 5383851 A **[0230]**
- US 5893397 A **[0230]**
- US 5466220 A **[0230]**
- US 5339163 A **[0230]**
- US 5312335 A **[0230]**
- US 5503627 A **[0230]**
- US 5064413 A **[0230]**
- US 5520639 A **[0230]**
- US 4596556 A **[0230]**
- US 4790824 A **[0230]**
- US 4941880 A **[0230]**
- US 4940460 A **[0230]**
- WO 9737705 A **[0230]**
- WO 9713537 PCT **[0230]**
- US 3845770 A **[0238]**
- US 3916899 A **[0238]**
- US 3536809 A **[0238]**
- US 3598123 A **[0238]**
- US 4008719 A **[0238]**
- US 5674533 A **[0238]**
- US 5059595 A **[0238]**
- US 5591767 A **[0238]**
- US 5120548 A **[0238]**
- US 5073543 A **[0238]**
- US 5639476 A **[0238]**
- US 5354556 A **[0238]**
- US 5639480 A **[0238]**
- US 5733566 A **[0238]**
- US 5739108 A **[0238]**
- US 5891474 A **[0238]**
- US 5922356 A **[0238]**
- US 5972891 A **[0238]**
- US 5980945 A **[0238]**
- US 5993855 A **[0238]**
- US 6045830 A **[0238]**
- US 6087324 A **[0238]**
- US 6113943 A **[0238]**
- US 6197350 B **[0238]**
- US 6248363 B **[0238]**
- US 6264970 B **[0238]**
- US 6267981 B **[0238]**
- US 6376461 B **[0238]**
- US 6419961 B **[0238]**
- US 6589548 B **[0238]**
- US 6613358 B **[0238]**
- US 6699500 B **[0238]**
- WO 2009088986 A **[0274] [0313]**
- WO 2009088880 A **[0274] [0313]**
- WO 2011008302 A **[0274] [0313] [0336]**
- WO 2011041399 A **[0279]**
- US 20100029693 A **[0279]**
- US 20100305096 A **[0279]**
- US 20100305084 A **[0279]**
- US 6800620 B **[0325]**
- US 20090012031 A **[0330]**
- US 20090203010 A **[0330]**
- US 20100222420 A **[0330]**
- US 20110251216 A **[0330]**
- US 20110286990 A **[0330]**
- US 20120014962 A **[0330]**
- US 20120071418 A **[0330]**
- US 20130040906 A **[0330]**
- US 20130195843 A **[0330]**
- US 20030113828 A **[0330]**
- US 20030158195 A **[0330]**
- US 20030229090 A **[0330]**
- US 20050075306 A **[0330]**
- US 20050232969 A **[0330]**
- US 20050267059 A **[0330]**
- US 20060205731 A **[0330]**
- US 20060247262 A **[0330]**
- US 20070219152 A **[0330]**
- US 20070219195 A **[0330]**

- US 20080114024 A **[0330]**
- US 20090171089 A **[0330]**
- US 20090306214 A **[0330]**
- US 20100048567 A **[0330]**
- US 20100152159 A **[0330]**
- US 20100152182 A **[0330]**
- US 20100316649 A **[0330]**
- US 20110053897 A **[0330]**
- US 20110112098 A **[0330]**
- US 20110245205 A **[0330]**
- US 20110275655 A **[0330]**
- US 20120027834 A **[0330]**
- US 20120093913 A **[0330]**
- US 20120101275 A **[0330]**
- US 20120130073 A **[0330]**
- US 20120142671 A **[0330]**
- US 20120184526 A **[0330]**
- US 20120220582 A **[0330]**
- US 20120277192 A **[0330]**
- US 20120309735 A **[0330]**
- US 20130040984 A **[0330]**
- US 20130090309 A **[0330]**
- US 20130116260 A **[0330]**
- US 20130165431 A **[0330]**
- US 7812164 B **[0331]**
- US 7230004 B **[0331]**
- US 20080293754 **[0331]**
- US 20080287420 **[0331]**
- US 20080293755 **[0331]**
- US 20020006931 A **[0331]**
- US 20070021493 A **[0331]**
- US 20070060546 A **[0331]**
- WO 200119800 A **[0331]**
- WO 200126644 A **[0331]**
- WO 200127135 A **[0331]**
- WO 200149279 A **[0331]**
- WO 200174344 A **[0331]**
- WO 2003011219 A **[0331]**
- WO 2003088970 A **[0331]**
- WO 2004020599 A **[0331]**
- WO 2005013800 A **[0331]**
- WO 2005033288 A **[0331]**
- WO 2005032343 A **[0331]**
- WO 2005042700 A **[0331]**
- WO 2006028958 A **[0331]**
- WO 2006050351 A **[0331]**
- WO 2006078283 A **[0331]**
- WO 2007054623 A **[0331]**
- WO 2007059157 A **[0331]**
- WO 2007120827 A **[0331]**
- WO 2007131201 A **[0331]**
- WO 2008070357 A **[0331]**
- WO 2008110611 A **[0331]**
- WO 2008112913 A **[0331]**
- WO 2008131354 A **[0331]**
- US 20100286114 **[0331]**
- US 20100093625 **[0331]**
- WO 09088990 A **[0336]**
- WO 09088086 A **[0336]**
- WO 2010036380 A **[0336]**
- WO 2010006086 A **[0336]**
- WO 09114870 A **[0336]**
- WO 05113556 A **[0336]**
- US 20090312310 A **[0336]**
- US 20110046165 A **[0336]**
- WO 9633172 A **[0343]**
- WO 9627583 A **[0343]**
- EP 97304971 **[0343]**
- EP 99308617 **[0343]**
- WO 9807697 A **[0343]**
- WO 9803516 A **[0343]**
- WO 9834918 A **[0343]**
- WO 9834915 A **[0343]**
- WO 9833768 A **[0343]**
- WO 9830566 A **[0343]**
- EP 606046 A **[0343]**
- EP 931788 A **[0343]**
- WO 9005719 A **[0343]**
- WO 9952910 A **[0343]**
- WO 9952889 A **[0343]**
- WO 9929667 A **[0343]**
- WO IB9801113 A **[0343]**
- EP 99302232 **[0343]**
- GB 9912961 A **[0343]**
- US 14846499 **[0343]**
- US 5863949 A **[0343]**
- US 5861510 A **[0343]**
- EP 780386 A **[0343]**
- WO 2013082540 A **[0464]**

Non-patent literature cited in the description

- **GAESTEL et al.** *Current Medicinal Chemistry,* 2007, vol. 14, 2214-2234 **[0002]**
- **EDGAR et al.** *Cancer Research,* 2010, vol. 70 (3), 1164-1172 **[0010]**
- *J. Pharmaceutical Sciences,* 1977, vol. 66, 1-19 **[0074]**
- Enantiomers, Racemates and Resolutions. Wiley Interscience, 1981 **[0090]**
- **WILEN et al.** Tetrahedron. 1977, vol. 33, 2725 **[0090]**
- Stereochemistry of Carbon Compounds. McGraw-Hill, 1962 **[0090]**
- Tables of Resolving Agents and Optical Resolutions. Univ. of Notre Dame Press, 1972, 268 **[0090]**
- Handbook of Chemistry and Physics **[0095]**
- **THOMAS SORRELL.** Organic Chemistry. University Science Books, 1999 **[0095]**
- **SMITH ; MARCH.** March's Advanced Organic Chemistry. John Wiley & Sons, Inc, 2001 **[0095]**

- **LAROCK.** Comprehensive Organic Transformations. VCH Publishers, Inc, 1989 **[0095]**
- **CARRUTHERS.** Some Modern Methods of Organic Synthesis. Cambridge University Press, 1987 **[0095]**
- **GREENE ; WUTS.** Protective Groups in Organic Synthesis. John Wiley & Sons, 2006 **[0112] [0128]**
- **T.H. GREENE ; P. G. M. WUTS.** Protective Groups in Organic Synthesis. John Wiley & Sons, 2006 **[0159]**
- Handbook of Clinical Drug Data. McGraw-Hill, 2002 **[0184]**
- Principles of Drug Action. Churchill Livingston, 1990 **[0184]**
- Basic and Clinical Pharmacology. McGraw Hill, 2011 **[0184]**
- The Pharmacological Basis of Therapeutics. McGraw Hill, 2001 **[0184]**
- Remingtons Pharmaceutical Sciences. Lippincott Williams & Wilkins, 2000 **[0184]**
- **MARTINDALE.** The Extra Pharmacopoeia. The Pharmaceutical Press, 1999 **[0184]**
- **SEFTON.** CRC Crit. Ref. Biomed. Eng. 1987, vol. 14, 201 **[0241]**
- **BUCHWALD et al.** *Surgery,* 1980, vol. 88, 507 **[0241]**
- **SAUDEK.** *N. Engl. J. Med.,* 1989, vol. 321, 574 **[0241]**
- **GOODSON.** *Medical Applications of Controlled Release,* 1984, vol. 2, 115-138 **[0241]**
- **LANGER.** *Science,* 1990, vol. 249, 1527-1533 **[0241]**
- **VANHAESEBROECK, B. et al.** *Annu Rev Biochem.,* 2001, vol. 70, 535-602 **[0256]**
- **FUNG-LEUNG WP.** *Cell Signal.,* 2011, vol. 23 (4), 603-8 **[0256]**
- **VANHAESEBROECK, B. et al.** *Current Topics in Microbiology and Immunology,* 2010 **[0259]**
- **HARRIS, SJ et al.** *Curr Opin Investig Drugs,* 2009, vol. 10 (11), 1151-62 **[0259]**
- **ROMMEL C. et al.** *Nat Rev Immunol,* 2007, vol. 7 (3), 191-201 **[0259]**
- **DURAND CA et al.** *J Immunol.,* 2009, vol. 183 (9), 5673-84 **[0259]**
- **DIL N ; MARSHALL AJ.** *Mol Immunol.,* 2009, vol. 46 (10), 1970-8 **[0259]**
- **AL-ALWAN MM et al.** *J Immunol.,* 2007, vol. 178 (4), 2328-35 **[0259] [0263]**
- **ZHANG TT et al.** *J Allergy Clin Immunol.,* 2008, vol. 122 (4), 811-819 **[0259] [0263]**
- **SRINIVASAN L et al.** *Cell,* 2009, vol. 139 (3), 573-86 **[0259]**
- **HIRSCH et al.** Central Role for G Protein-Coupled Phosphoinositide 3-Kinase γ in Inflammation. *Science,* 2000, vol. 287, 1049-1053 **[0260] [0266]**
- **SASAKI et al.** Function of PI3Kγ in Thymocyte Development, T Cell Activation, and Neutrophil Migration. *Science,* 2000, vol. 287, 1040-1046 **[0260] [0266]**
- **LI et al.** Roles of PLC-β2 and -β3 and PI3Kγ in Chemoattractant-Mediated Signal Transduction. *Science,* 2000, vol. 287, 1046-1049 **[0260] [0266]**
- **RANDIS et al.** *Eur. J. Immunol.,* 2008, vol. 38 (5), 1215-24 **[0260]**
- **TAKEDA et al.** *J Allergy Clin. Immunol.,* 2009, vol. 123, 805-12 **[0260]**
- **SASAKI.** *Science,* 2000, vol. 287, 1040-46 **[0260]**
- **COMERFOLD.** *PLOS One,* 2012, vol. 7, e45095 **[0260] [0262]**
- **ROLLER et al.** Blockade of Phosphatidylinositol 3-Kinase (PI3K)δ or PI3Kγ Reduces IL-17 and Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis. *J. Immunol.,* 2012, vol. 189, 4612-4620 **[0260] [0266]**
- **SCHMID et al.** *Cancer Cell,* 2011, vol. 19, 715-27 **[0260] [0261]**
- **SUBRAMANIAM et al.** *Cancer Cell,* 2012, vol. 21, 459-472 **[0260]**
- **BURGER.** Inhibiting B-Cell Receptor Signaling Pathways in Chronic Lymphocytic Leukemia. *Curr. Memato. Malig. Rep.,* 2012, vol. 7, 26-33 **[0260] [0267]**
- **RUCKLE et al.** *Nature Rev., Drug Discovery,* 2006, vol. 5, 903-18 **[0261]**
- **SCHMID et al.** Myeloid cells in tumor inflammation. *Vascular Cell,* 2012 **[0261]**
- **COMERFORD et al.** *PLOS One,* 2012, vol. 7, e45095 **[0261] [0262]**
- **SASAKI et al.** *Science,* 2000, vol. 287, 1040-46 **[0261]**
- **TAKEDA et al.** *J. Allergy Clin. Immunol,* 2009, vol. 123, 805-12 **[0261] [0262]**
- **LI et al.** *Science,* 2000, vol. 287, 1046-49 **[0261]**
- **HIRSCH et al.** *Science,* 2000, vol. 287, 1049-53 **[0261]**
- **EDLING et al.** *Human Cancer Biology,* 2010, vol. 16 (2), 4928-37 **[0261]**
- **KYBURZ.** *Springer Semin. Immunopathology,* 2003, vol. 25, 79-90 **[0262]**
- **RANDIS.** *Eur. J. Immunol.,* 2008, vol. 38 (5), 1215-24 **[0262]**
- **LEE et al.** *FASEB J.,* 2006, vol. 20, 455-65 **[0262]**
- **HAYLOCK-JACOB et al.** *J. Autoimmunity,* 2011, vol. 36, 278-87 **[0262]**
- **SCHMID et al.** *Cancer Cell,* 2011, vol. 19 (6), 715-27 **[0262]**
- **SUBRAMANIAM et al.** *Cancer Cell,* 2012, vol. 21, 459-72 **[0262]**
- **CLAYTON E et al.** *J Exp Med.,* 2002, vol. 196 (6), 753-63 **[0263]**
- **BILANCIO A et al.** *Blood,* 2006, vol. 107 (2), 642-50 **[0263]**
- **OKKENHAUG K. et al.** *Science,* vol. 297 (5583), 1031-4 **[0263]**
- **SRINIVASANL et al.** *Cell,* 2009, vol. 139 (3), 573-86 **[0263]**
- **GARÇON F. et al.** *Blood,* 2008, vol. 111 (3), 1464-71 **[0264]**

- **OKKENHAUG K et al.** *J Immunol.,* 2006, vol. 177 (8), 5122-8 **[0264]**
- **SOOND DR et al.** *Blood,* 2010, vol. 115 (11), 2203-13 **[0264]**
- **REIF K.** *J Immunol. 2004,* 2004, vol. 173 (4), 2236-40 **[0264]**
- **JI H. et al.** *Blood,* 2007, vol. 110 (8), 2940-7 **[0264]**
- **WEBB LM et al.** *J Immunol.,* 2005, vol. 175 (5), 2783-7 **[0264]**
- **LIU D et al.** *J Immunol.,* 2010, vol. 184 (6), 3098-105 **[0264]**
- **HAYLOCK-JACOBS S et al.** *J Autoimmun.,* 2011, vol. 36 (3-4), 278-87 **[0264]**
- **JARMIN SJ et al.** *J Clin Invest.,* 2008, vol. 118 (3), 1154-64 **[0264]**
- **PURI ; GOLD.** Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory disease and B-cell malignancies. *Front. Immunol.,* 2012, vol. 3, 256 **[0266] [0267]**
- **BUITENHUIS et al.** The role of the PI3k-PKB signaling module in regulation of hematopoiesis. *Cell Cycle,* 2009, vol. 8 (4), 560-566 **[0266]**
- **HOELLENRIEGEL ; BURGER.** Phosphoinositide 3'-kinase delta: turning off BCR signaling in Chronic Lymphocytic Leukemia. *Oncotarget,* 2011, vol. 2 (10), 737-738 **[0266]**
- **HIRSCH et al.** Central Role for G Protein-Coupled Phosphoinositide 3-Kinase y in Inflammation. *Science,* 2000, vol. 287, 1049-1053 **[0266]**
- **CUSHING et al.** PI3Kδ and PI3Kγ as Targets for Autoimmune and Inflammatory Diseases. *J. Med. Chem.,* 2012, vol. 55, 8559-8581 **[0266]**
- **MAXWELL et al.** Attenuation of phosphoinositide 3-kinase δ signaling restrains autoimmune disease. *J. Autoimmun.,* 2012, vol. 38, 381-391 **[0266]**
- **HAYLOCK-JACOBS et al.** PI3Kδ drives the pathogenesis of experimental autoimmune encephalomyelitis by inhibiting effector T cell apoptosis and promoting Th17 differentiation. *J. Autoimmun.,* 2011, vol. 36, 278-287 **[0266]**
- **SOOND et al.** PI3K p110δ regulates T-cell cytokine production during primary and secondary immune responses in mice and humans. *Blood,* 2010, vol. 115 (11), 2203-2213 **[0266]**
- **CAMPS et al.** Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis. *Nat. Med.,* 2005, vol. 11 (9), 936-943 **[0266]**
- **MAXWELL.** Attenuation of phosphoinositide 3-kinase δ signaling restrains autoimmune disease. *J. Autoimmun.,* 2012, vol. 38, 381-391 **[0266]**
- **SUBRAMANIAM et al.** Targeting Nonclassical Oncogenes for Therapy in T-ALL. *Cancer Cell,* 2012, vol. 21, 459-472 **[0267]**
- **LANNUTTI et al.** CAL-101 a p110δ selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. *Blood,* 2011, vol. 117 (2), 591-594 **[0267]**
- **HOELLENRIEGEL et al.** The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leuckemia. *Blood,* 2011, vol. 118 (13), 3603-3612 **[0267]**
- **HERISHANU et al.** The lymph node microenvironment promotes B-cell receptor signaling, NF-κB activation, and tumor proliferation in chronic lymphocytic leukemia. *Blood,* 2011, vol. 117 (2), 563-574 **[0267]**
- **DAVIS et al.** Chronic active B-cell-receptor signaling in diffuse large B-cell lymphoma. *Nature,* 2010, vol. 463, 88-92 **[0267]**
- **PIGHI et al.** Phospho-proteomic analysis of mantle cell lymphoma cells suggests a pro-survival role of B-cell receptor signaling. *Cell Oncol. (Dordr),* 2011, vol. 34 (2), 141-153 **[0267]**
- **RIZZATTI et al.** Gene expression profiling of mantle cell lymphoma cells reveals aberrant expression of genes from the PI3K-AKT, WNT and TGFβ signaling pathways. *Brit. J. Haematol.,* 2005, vol. 130, 516-526 **[0267]**
- **MARTINEZ.** The Molecular Signature of Mantle Cell Lymphoma Reveals Multiple Signals Favoring Cell Survival. *Cancer Res.,* 2003, vol. 63, 8226-8232 **[0267]**
- **HERISHANU.** The lymph node microenvironment promotes B-cell receptor signaling, NF-κB activation, and tumor proliferation in chronic lymphocytic leukemia. *Blood,* 2011, vol. 117 (2), 563-574 **[0267]**
- **KURTOVA.** Diverse marrow stromal cells protect CLL cells from spontaneous and drig-induced apoptosis: development of a reliable and reproducible system to assess stromal cell adhesion-mediated drug resistance. *Blood,* 2009, vol. 114 (20), 4441-4450 **[0267]**
- **BURGER.** High-level expression of the T-cell chemokines CCL3 and CCL4 by chronic lymphocytic leukemia B cells in nurselike cell cocultures and after BCR stimulation. *Blood,* 2009, vol. 113 (13), 3050-3058 **[0267]**
- **QUIROGA.** B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406. *Blood,* 2009, vol. 114 (5), 1029-1037 **[0267]**
- **SUBRAMANTAM et al.** Targeting Nonclassical Oncogenes for Therapy in T-ALL. *Cancer Cell,* 2012, vol. 21, 459-472 **[0268]**
- **NISITANI.** Posttranscriptional regulation of Bruton's tyrosine kinase expression in antigen receptor-stimulated splenic B cells. *PNAS,* 2000, vol. 97 (6), 2737-2742 **[0268]**

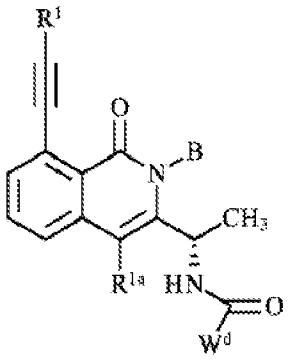
- **DE WEERS.** The Bruton's tyrosine kinase gene is expressed throughout B cell differentiation, from early precursor B cell stages preceding immunoglobulin gene rearrangement up to mature B cell stages. *Eur. J. Immunol.,* 1993, vol. 23, 3109-3114 **[0268]**
- **SMITH et al.** Expression of Bruton's Agammaglobulinemia Tyrosine Kinase Gene, BTK, Is Selectively Down-Regulated in T Lymphocytes and Plasma Cells. *J. Immunol.,* 1994, vol. 152, 557-565 **[0268]**
- **RANDIS TM et al.** *Eur J Immunol.,* 2008, vol. 38 (5), 1215-24 **[0269] [0270]**
- **PINHO V.** *J Immunol.,* 2007, vol. 179 (11), 7891-8 **[0269]**
- **SADHU C. et al.** *J Immunol.,* 2003, vol. 170 (5), 2647-54 **[0269]**
- **CONDLIFFE AM et al.** *Blood,* 2005, vol. 106 (4), 1432-40 **[0269]**
- **KULKARNI.** *Immunology,* 2011, vol. 4 (168), 1-11 **[0269]**
- **MARWICK JA et al.** *Am J Respir Crit Care Med.,* 2009, vol. 179 (7), 542-8 **[0270]**
- **KONRAD S et al.** *J Biol Chem.,* 2008, vol. 283 (48), 33296-303 **[0270]**
- **ALI K et al.** *Nature,* 2004, vol. 431 (7011), 1007-11 **[0271]**
- **LEE KS et al.** *FASEB J.,* 2006, vol. 20 (3), 455-65 **[0271] [0277]**
- **KIM MS et al.** *Trends Immunol.,* 2008, vol. 29 (10), 493-501 **[0271]**
- **GUO H et al.** *J Exp Med.,* 2008, vol. 205 (10), 2419-35 **[0272]**
- **TASSI I et al.** *Immunity,* 2007, vol. 27 (2), 214-27 **[0272]**
- **SAUDEMONT A.** *Proc Natl Acad Sci US A.,* 2009, vol. 106 (14), 5795-800 **[0272]**
- **KIM N et al.** *Blood,* 2007, vol. 110 (9), 3202-8 **[0272]**
- **WILLIAMS, O. et al.** *Chem Biol,* 2010, vol. 17 (2), 123-34 **[0274]**
- **BARTOK et al.** *Arthritis Rheum,* 2010, vol. 62 (10), 362 **[0274]**
- **HAYLOCK-JACOBS, S. et al.** *J. Autoimmunity,* 2011, vol. 36 (3-4), 278-87 **[0275]**
- **BARBER, DF et al.** *J. Immunol.,* 2006, vol. 176 (1), 589-93 **[0276]**
- **ALI K et al.** *J Immunol.,* 2008, vol. 180 (4), 2538-44 **[0277]**
- **ALI K.** *Nature,* 2004, vol. 431 (7011), 1007-11 **[0277]**
- **LEE KS et al.** *J Allergy Clin Immunol,* 2006, vol. 118 (2), 403-9 **[0277]**
- **DOUKAS J et al.** *J Pharmacol Exp Ther.,* 2009, vol. 328 (3), 758-65 **[0278]**
- **VOGT, PK et al.** *Curr Top Microbiol Immunol.,* 2010, vol. 347, 79-104 **[0279]**
- **FRESNO VARA, JA et al.** *Cancer Treat Rev.,* 2004, vol. 30 (2), 193-204 **[0279]**
- **ZHAO, L ; VOGT, PK.** *Oncogene,* 2008, vol. 27 (41), 5486-96 **[0279]**
- **COURTNEY, KD et al.** *J Clin Oncol.,* 2010, vol. 28 (6), 1075-1083 **[0279]**
- **MARKMAN, B et al.** *Ann Oncol.,* 2010, vol. 21 (4), 683-91 **[0279]**
- **KONG, D ; YAMORI, T.** *Curr Med Chem.,* 2009, vol. 16 (22), 2839-54 **[0279]**
- **JIMENO, A et al.** *J Clin Oncol.,* 2009, vol. 27, 156s **[0279]**
- **FLINN, IW et al.** *J Clin Oncol.,* 2009, vol. 27, 156s **[0279]**
- **SHAPIRO, G et al.** *J Clin Oncol.,* 2009, vol. 27, 146s **[0279]**
- **WAGNER, AJ et al.** *J Clin Oncol.,* 2009, vol. 27, 146s **[0279]**
- **VOGT, PK et al.** *Virology,* 2006, vol. 344 (1), 131-8 **[0279]**
- **WARD, S et al.** *Chem Biol.,* 2003, vol. 10 (3), 207-13 **[0279]**
- **SALMENA, L et al.** *Cell,* 2008, vol. 133, 403-414 **[0280]**
- **CHAPUIS, N et al.** *Clin Cancer Res.,* 2010, vol. 16 (22), 5424-35 **[0280]**
- **KHWAJA, A.** *Curr Top Microbiol Immunol.,* 2010, vol. 347, 169-88 **[0280]**
- **HERRERA, VA et al.** *Anticancer Res.,* 2011, vol. 31 (3), 849-54 **[0280]**
- **HALUSKA, F et al.** *Semin Oncol.,* 2007, vol. 34 (6), 546-54 **[0280]**
- **SARKER, D et al.** *Clin Cancer Res.,* 2009, vol. 15 (15), 4799-805 **[0280]**
- **CHEN, JS et al.** *Mol Cancer Ther.,* 2008, vol. 7, 841-850 **[0280]**
- **BANSAL, N et al.** *Cancer Control.,* 2009, vol. 16 (1), 8-13 **[0280]**
- **FURUKAWA, T.** *J Gastroenterol.,* 2008, vol. 43 (12), 905-11 **[0280]**
- **PORTA, C ; FIGLIN, RA.** *J Urol.,* 2009, vol. 182 (6), 2569-77 **[0280]**
- **SAIF, MW ; CHU, E.** *Cancer J.,* 2010, vol. 16 (3), 196-201 **[0280]**
- **TORBETT, NE et al.** *Biochem J.,* 2008, vol. 415, 97-100 **[0280]**
- **MAZZOLETTI, M ; BROGGINI, M.** *Curr Med Chem.,* 2010, vol. 17 (36), 4433-47 **[0280]**
- **CHEN J.S. et al.** *Mol Cancer Ther.,* 2008, vol. 7 (4), 841-50 **[0281]**
- **IKEDA H. et al.** *Blood,* 2010, vol. 116 (9), 1460-8 **[0281]**
- **BILLOTTET C et al.** *Oncogene,* 2006, vol. 25 (50), 6648-59 **[0282]**
- **BILLOTTET C et al.** *Cancer Res.,* 2009, vol. 69 (3), 1027-36 **[0282]**
- **MEADOWS, SA.** *52nd Annual ASH Meeting and Exposition,* 04 December 2010 **[0282]**
- **IKEDA H et al.** *Blood,* 2010, vol. 116 (9), 1460-8 **[0282]**
- **HERMAN SE et al.** *Blood,* 2010, vol. 116 (12), 2078-88 **[0282]**

- **HERMAN SE et al.** *Blood,* 2011, vol. 117 (16), 4323-7 **[0282]**
- **FURMAN, RR et al.** *52nd Annual ASH Meeting and Exposition,* 04 December 2010 **[0284]**
- **HOELLENRIEGEL, J et al.** *52nd Annual ASH Meeting and Exposition,* 04 December 2010 **[0284] [0286]**
- **WEBB, HK et al.** *52nd Annual ASH Meeting and Exposition,* 04 December 2010 **[0284]**
- **MEADOWS et al.** *52nd Annual ASH Meeting and Exposition,* 04 December 2010 **[0284]**
- **KAHL, B et al.** *52nd Annual ASH Meeting and Exposition,* 04 December 2010 **[0284]**
- **LANNUTTI BJ et al.** *Blood,* 2011, vol. 117 (2), 591-4 **[0284]**
- **KASHISHIAN A et al.** *Poster presented at: The American Association of Cancer Research 102nd Annual Meeting,* 02 April 2011 **[0285]**
- **WARD S et al.** *Chem Biol.,* 2003, vol. 10 (3), 207-13 **[0285]**
- **MEADOWS, SA et al.** *Paper presented at: 52nd Annual ASH Meeting and Exposition,* 04 December 2010 **[0287]**
- **GENGL et al.** *Cancer Res.,* 2004, vol. 64 (14), 4893-9 **[0287]**
- **SCHMID et al.** *Cancer Cell,* 2011, vol. 19, 715-727 **[0289]**
- **CIRAOLO et al.** *Molecular Biology of the Cell,* 2010, vol. 21, 704-711 **[0291]**
- **WISLER et al.** *Amgen SOT, Abstract ID # 2334,* 2012 **[0291]**
- **BI et al.** *J Biol Chem,* 1999, vol. 274, 10963-10968 **[0291]**
- **KULKARNI et al.** *Science,* 2000, vol. 287, 1049-1053 **[0291]**
- **LEE et al.** *J Allergy Clin Immunol,* 2006, vol. 118 (2), 403-9 **[0313]**
- **WILLIAMS et al.** *Chem Biol,* 2010, vol. 17 (2), 123-34 **[0313]**
- **CHEVALIER et al.** *Kidney International,* 2009, vol. 75, 1145-1152 **[0313]**
- **MOORE ; HOGABOAM.** *Am. J. Physiol. Lung. Cell. Mol. Physiol.,* 2008, vol. 294, L152-L160 **[0313]**
- **CHUANG et al.** *Clin Liver Dis,* 2008, vol. 12, 333-347 **[0313]**
- **OMENETTI, A. et al.** *Laboratory Investigation,* 2007, vol. 87, 499-514 **[0313]**
- **VARICCHIO, L. et al.** *Expert Rev. Hematol.,* 2009, vol. 2 (3), 315-334 **[0313]**
- **S. M. ELBASHIR et al.** *Nature,* 2001, vol. 411, 494-498 **[0330]**
- **VON HOFF D. et al.** *N. Engl. J. Med.,* 2009, vol. 361 (12), 1164-72 **[0331]**
- **ROBARGE K.D. et al.** *Bioorg Med Chem Lett.,* 2009, vol. 19 (19), 5576-81 **[0331]**
- **YAUCH, R. L. et al.** *Science,* 2009, vol. 326, 572-574 **[0331]**
- *Sciencexpress,* 1-3 **[0331]**
- **RUDIN, C. et al.** *New England J of Medicine,* 2009, 361-366 **[0331]**
- **SIU L. et al.** *J. Clin. Oncol.,* 2010, vol. 28, 15s **[0331]**
- **PAN S. et al.** *ACS Med. Chem. Lett.,* 2010, vol. 1 (3), 130-134 **[0331]**
- **ROMINGER C.M. et al.** *J. Pharmacol. Exp. Ther.,* 2009, vol. 329 (3), 995-1005 **[0331]**
- **LUCAS B.S. et al.** *Bioorg. Med. Chem. Lett.,* 2010, vol. 20 (12), 3618-22 **[0331]**
- **GOODMAN ; GILMAN'S.** The Pharmacological Basis of Therapeutics **[0370]**
- *Cancer Cell,* 2005, vol. 7, 468 **[0571]**
- *Cancer Res.,* 1984, vol. 44, 717-726 **[0572]**
- *Science,* 2010, vol. 330, 827 **[0574]**
- *Current Protocols in Immunology Unit 20.2,* 2000 **[0575]**
- *PNAS,* 2010, vol. 107, 4275 **[0577]**
- *Rapid Commun. Mass Spectrom.,* vol. 10, 1019-1026 **[0579]**
- *Methods Enzymol.,* 2007, vol. 434, 131-54 **[0582]**
- **S. BOLLAND ; J.V. RAVTECH.** *Immunity,* 2000, vol. 12, 277-285 **[0588]**
- **T. WU et al.** *J. Clin Invest.,* vol. 117, 2186-2196 **[0589]**
- *Nature Medicine,* 2008, vol. 14, 748-755 **[0590]**
- *Cancer Genet Cytogenet,* August 2005, vol. 161 (1), 51-6 **[0593]**
- **NIALS et al.** *Dis Model Mech.,* 2008, vol. 1 (4-5), 213-220 **[0612]**
- **BOEHNCKE et al.** *Clinics in Dermatology,* 2007, vol. 25, 596-605 **[0615]**
- **HONG et al.** *J Immunol.,* 1999, vol. 162, 7480-7491 **[0616]**
- **YAMAMOTO et al.** *J Invest Dermatol,* 1999, vol. 112, 456-462 **[0617]**
- **HARGIS et al.** *AJP,* 1985, vol. 120 (2), 323-325 **[0620]**
- **PHYANAGI et al.** *Arthritis & Rheumatism,* 2009, vol. 60 (10), 3118-3127 **[0620]**
- **CHIORINI et al.** *Journal of Autoimmunity,* 2009, vol. 33, 190-196 **[0623]**
- **JONSSON et al.** *Clin Immunol Immunopathol,* 1987, vol. 42, 93-101 **[0623]**
- **DESHMUKH et al.** *J Oral Pathol Med,* 2009, vol. 38, 42-27 **[0623]**
- **CHA et al.** *Arthritis Rheum,* 2002, vol. 46, 1390-1398 **[0623]**
- **KONG et al.** *Clin Exp Rheumatol,* 1998, vol. 16, 675-681 **[0623]**
- **PODOLIN et al.** *J Exp Med,* 1993, vol. 178, 793-803 **[0623]**
- **RASOOLY et al.** *Clin Immunol Immunopathol,* 1996, vol. 81, 287-292 **[0623]**
- **LI et al.** *Immunity,* 2004, vol. 21, 551-560 **[0623]**
- **OAK et al.** *Proc Natl Acad Sci USA,* 2006, vol. 103, 16882-16887 **[0623]**
- **GROOM et al.** *J Clin Invest,* 2002, vol. 109, 59-68 **[0623]**

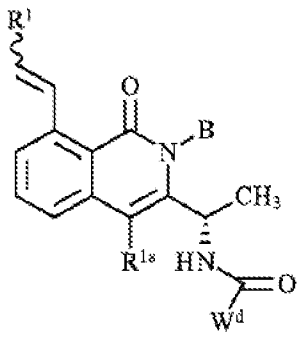
- **OH-HORA et al.** *Nat. Immunol,* 2008, vol. 9, 432-443 **[0623]**
- **NISHIMORI et al.** *J Immunol,* 1995, vol. 154, 4865-4873 **[0623]**
- **SHEN et al.** *J Immunol,* 2006, vol. 177, 5676-5686 **[0623]**
- **MCGRATH-MORROW et al.** *Am J Physiol Lung Cell MolPhysiol,* 2006, vol. 291, L837-846 **[0623]**
- **KONRAD et al.** *Journal of Biological Chemistry,* 2008, vol. 283 (48), 33296-33303 **[0624]**
- **HE et al.** *Leukemia Research,* 2009, vol. 33, 798-802 **[0628]**
- **CAMPS et al.** *Nature Medicine,* 2005, vol. 11 (9), 936-943 **[0630]**

Patentkrav

1. Forbindelse med Formel (I) eller Formel (A):



Formel (I) eller



Formel (A)

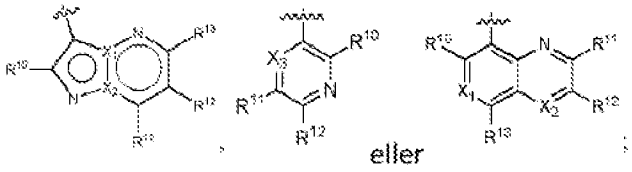
hvor:

R^1 er hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -COR^2, -$COOR^3$ eller -$CONR^4R^5$;

B er hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -COR^2, -$COOR^3$, -$CONR^4R^5$ eller -$Si(R^6)_3$;

hvor R^2, R^3, R^4, R^5 og R^6 hver især, uafhængigt, er hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl eller heteroaryl;

W^d er



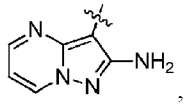
eller

hvor

X_1, X_2 og X_3 hver især uafhængigt er C, CR^{13} eller N; og

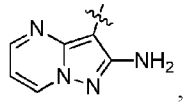
R^{10}, R^{11}, R^{12} og R^{13} hver især uafhængigt er hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphat, urinstof, carbonat eller NR'R"

hvor R' og R'' sammen med det nitrogen, som de er bundet til, danner en cyklisk enhed;
hvor R^{1a} er hydrogen, halo, alkyl, alkenyl, alkynyl eller CN;
hvor hver alkyl, alkenyl eller alkynyl er eventuelt substitueret med en eller flere halo, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, $S(O)$(alkyl), $S(O)_2$(alkyl), cycloalkyl, heterocycloalkyl, aryl eller heteroaryl;
hvor hver cycloalkyl, heterocycloalkyl, aryl eller heteroaryl er eventuelt substitueret med en eller flere halo, alkyl, alkenyl, alkynyl, OH, alkoxy, oxo, NH_2, NH(alkyl), $N(alkyl)_2$, COH, CO(alkyl), COOH, COO(alkyl), $CONH_2$, CONH(alkyl), $CON(alkyl)_2$, $S(O)$(alkyl) eller $S(O)_2$(alkyl);
hvor, i Formel (I), når R^{1a} er H, B er usubstitueret phenyl, og W^d er



,

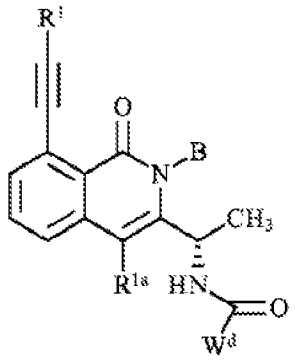
så er R^1 ikke hydrogen, methyl, $(CH_2)NH_2$ eller $(CH_2)_2NH_2$;
hvor, i Formel (A), når R^{1a} er H, B er usubstitueret phenyl, og W^d er



,

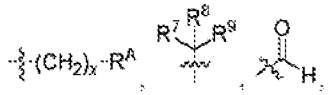
Så er R^1 ikke phenyl;
eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller en farmaceutisk acceptabel form deraf.

2. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1, hvor forbindelsen er en forbindelse med Formel (I):



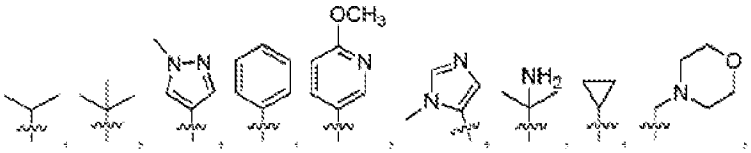
Formel (I).

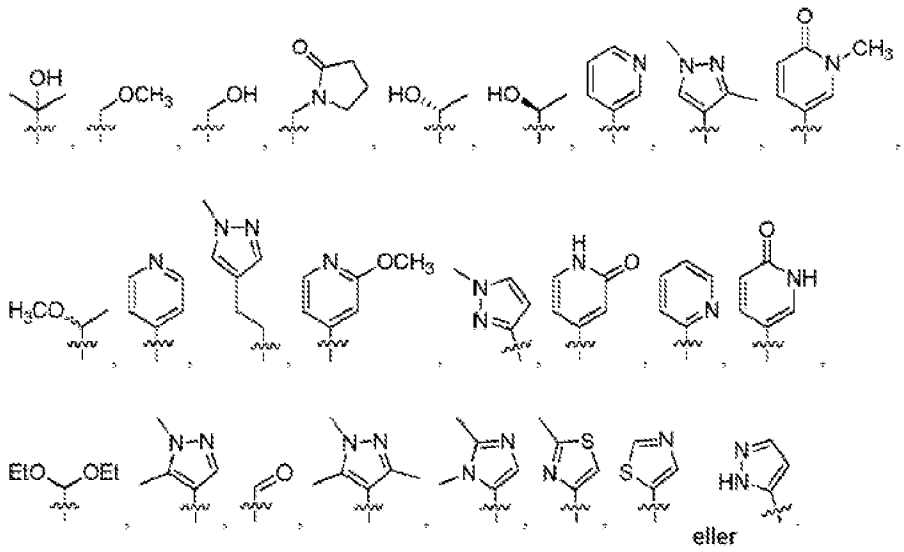
3. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1 eller 2, hvor R^1 er forgrenet alkyl, 5- eller 6-leddet aryl, 5- eller 6-leddet heteroaryl, 5- eller 6-leddet cycloalkyl, eller 5- til 6-leddet heterocycloalkyl,



cyclopropyl eller methyl;
hvor R^A er OH, alkoxy, cycloalkyl, heterocycloalkyl, aryl eller heteroaryl;
x er 1, 2, 3, 4, 5 eller 6; og
R^7, R^8 og R^9 hver især, uafhængigt, er hydrogen, OH, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, alkyl, cycloalkyl, heterocycloalkyl, aryl eller heteroaryl.

4. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1 eller 2; hvor R^1 er: methyl,





eller

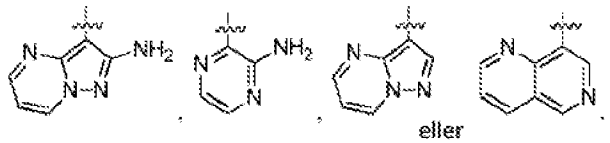
5. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1 eller 2, hvor R^1 er en 5- til 10-leddet heteroaryl, fortrinsvis en 6-leddet heteroaryl, mere fortrinsvis pyridinyl eller pyrimidinyl; eller en 5-leddet heteroaryl, fortrinsvis thiazolyl, pyrazolyl eller imidazolyl; hvor heteroarylen er eventuelt substitueret med en eller flere alkylgrupper.

6. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-5, hvor B er aryl, heteroaryl, cycloalkyl; fortrinsvis 3- til 6-leddet cycloalkyl; mere fortrinsvis

eller heterocycloalkyl.

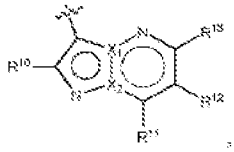
7. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 6, hvor B er usubstitueret phenyl, eller phenyl substitueret med 1, 2 eller 3 forekomst(er) af R^z; hvor hver forekomst af R^z er uafhængigt halo eller alkyl.

8. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-7, hvor W^d er



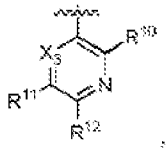
9. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-7; hvor:

W^d er



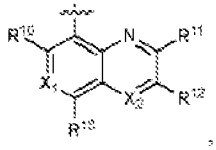
hvor en af X_1 og X_2 er C og den anden er N; eller

W^d er



hvor X_3 er N eller CR^{13}; eller

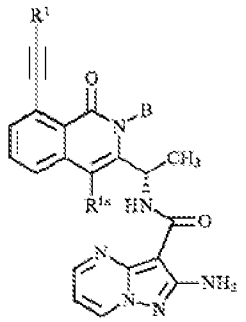
W^d er



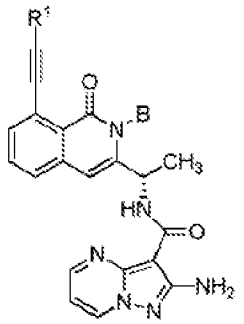
hvor en af X_1 og X_2 er N og den anden er CR^{13}.

10. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller en farmaceutisk acceptabel form deraf ifølge et af kravene 1-9, hvor R^{1a} er H.

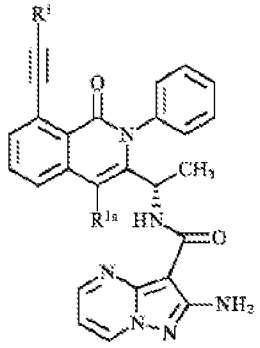
11. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 2, hvor forbindelsen er en forbindelse med formel II, III, V, VI, VIII, IX eller XII:



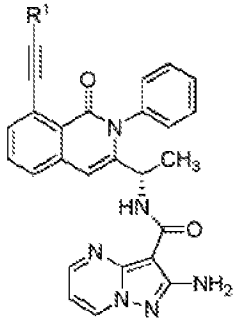
II,



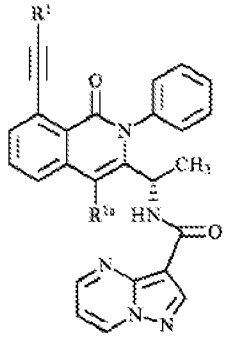
III,



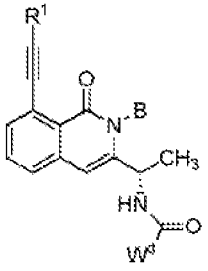
V,



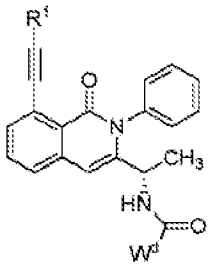
VI,



VIII,

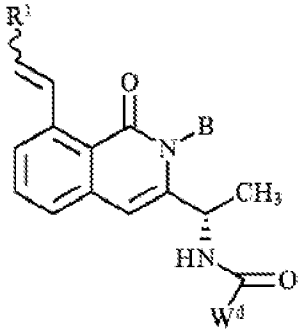


IX eller



XII.

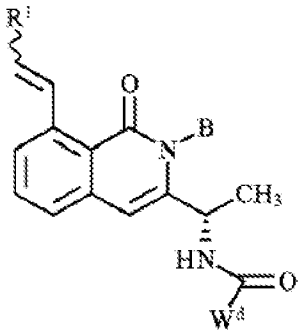
12. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1, hvor forbindelsen er en forbindelse med Formel (A):



Formel (A)

og R^1 er alkyl.

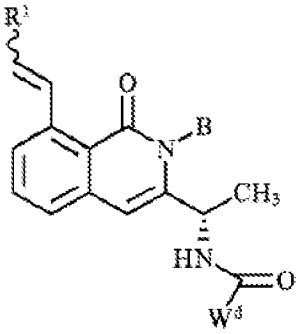
13. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1, hvor forbindelsen er en forbindelse med Formel (A):



Formel (A)

og R^1 er heteroaryl.

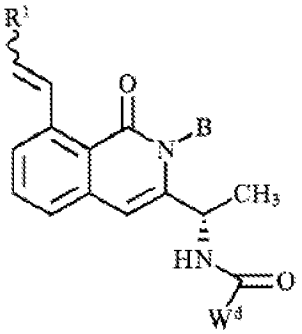
14. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1, krav 12 eller krav 13; hvor forbindelsen er en forbindelse med Formel (A):



Formel (A)

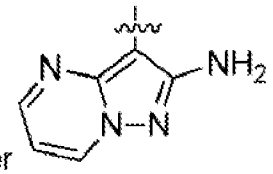
og B er phenyl.

15. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1 ifølge et af kravene 12-14; hvor forbindelsen er en forbindelse med Formel (A):



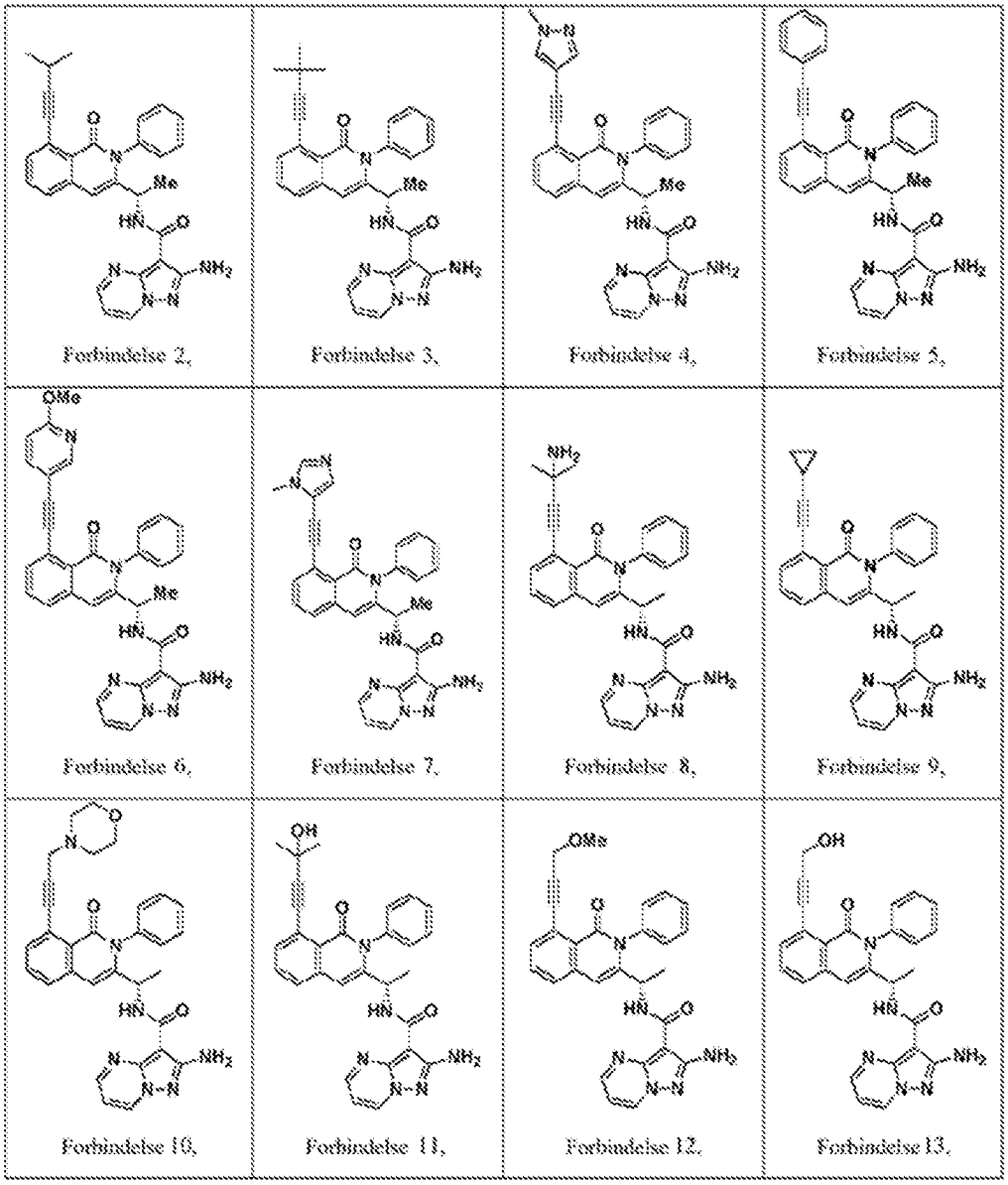
Formel (A)

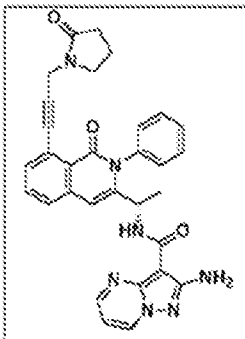
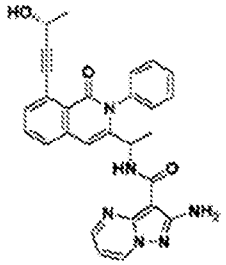
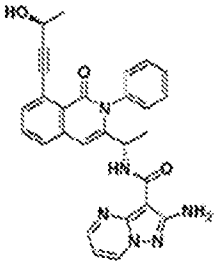
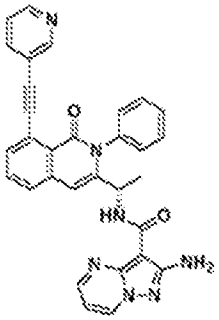
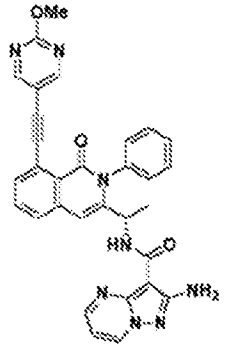
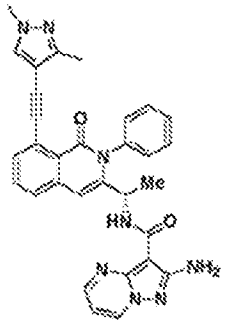
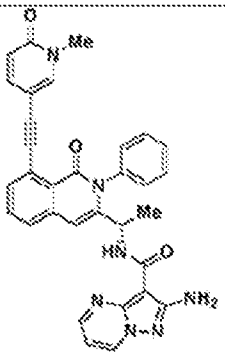
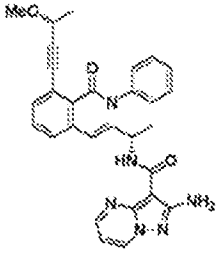
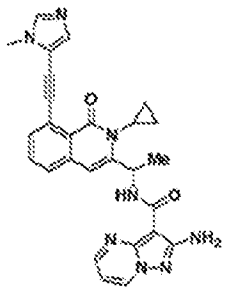
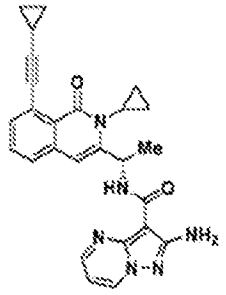
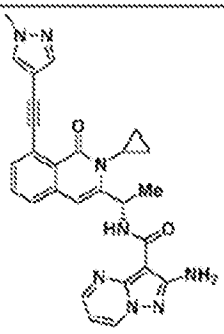
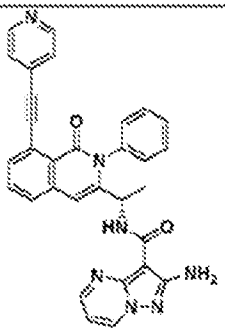
og W^d er

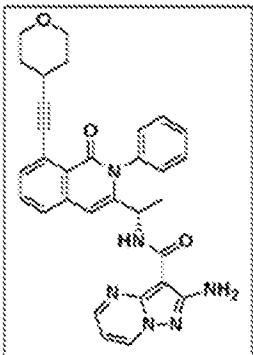
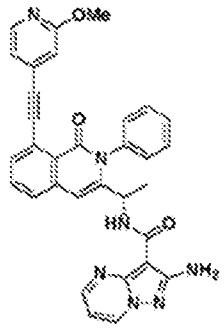
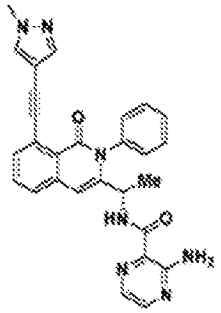
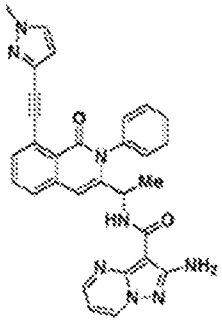
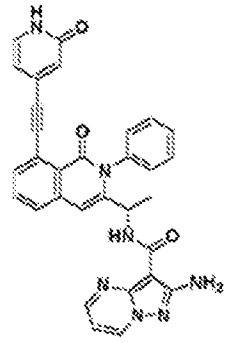
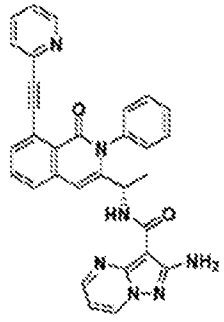
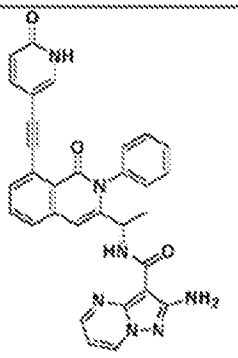
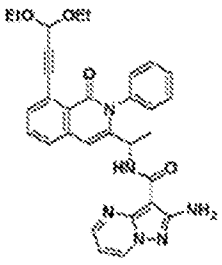
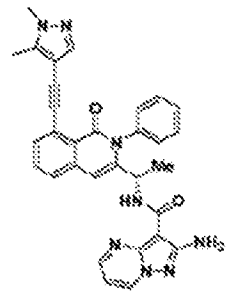
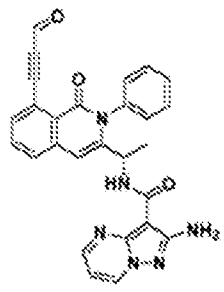
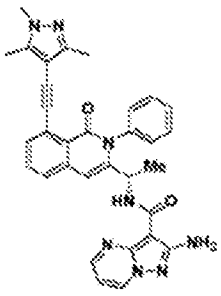
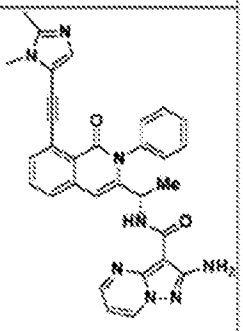


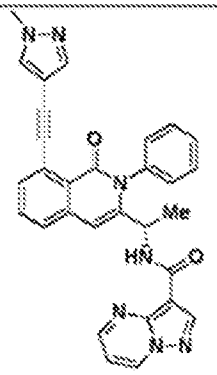
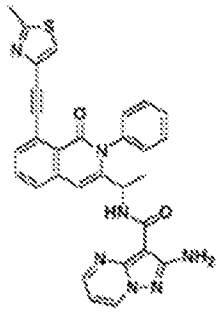
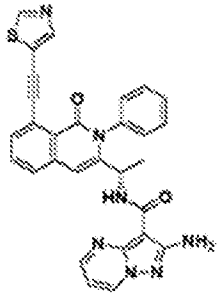
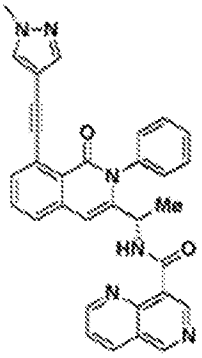
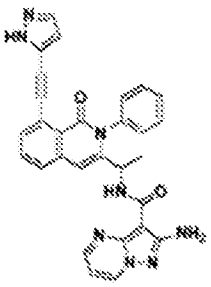
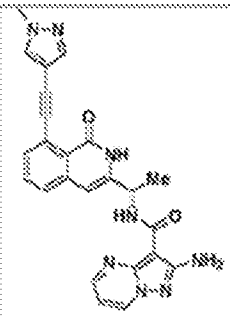
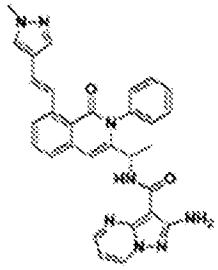
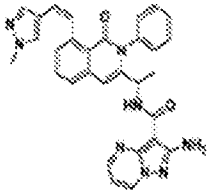
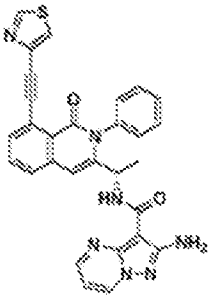
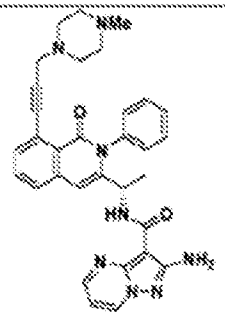
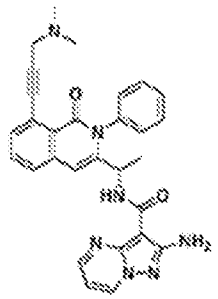
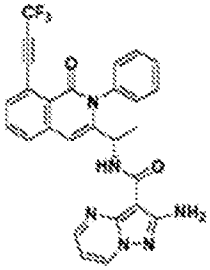
16. Forbindelse, eller en enantiomer, en blanding af enantiomerer, eller en blanding af to eller flere diastereomerer deraf, eller farmaceutisk acceptabel form deraf ifølge krav 1, hvor forbindelsen er en (S)-stereokemisk konfiguration, fortrinsvis med en enantiomerisk renhed på mere end 75 %.

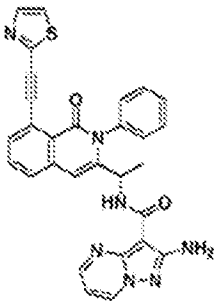
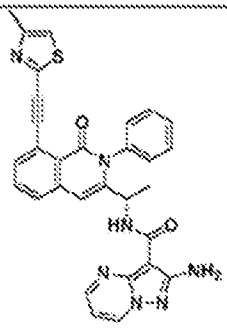
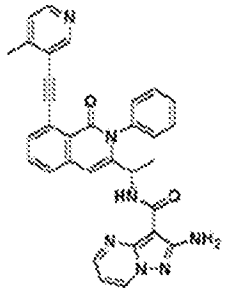
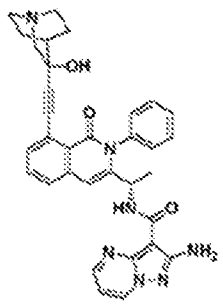
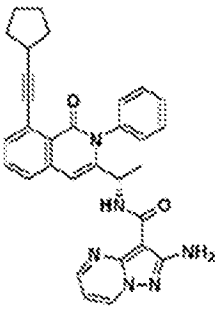
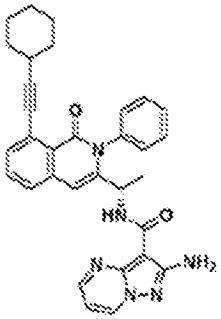
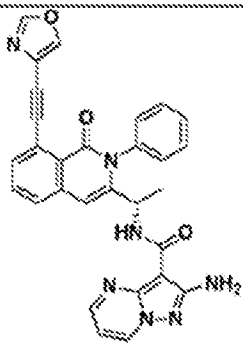
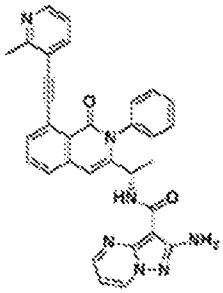
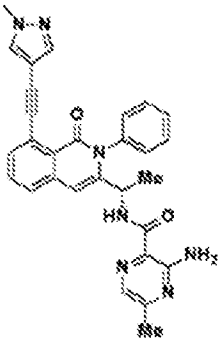
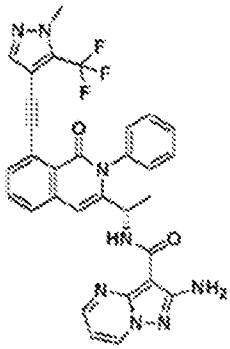
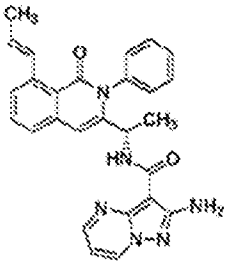
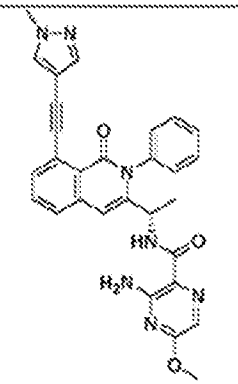
17. Forbindelse ifølge krav 1, som er:

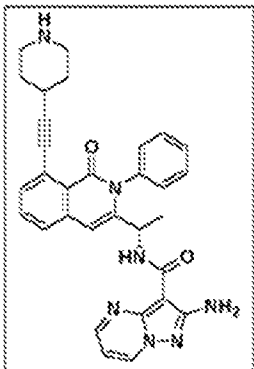
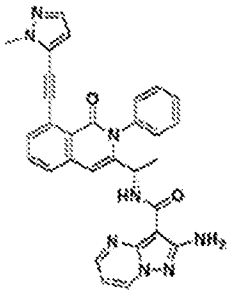
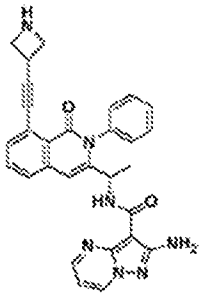
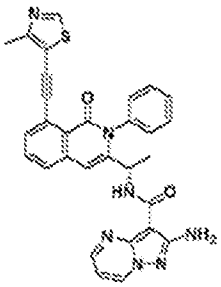
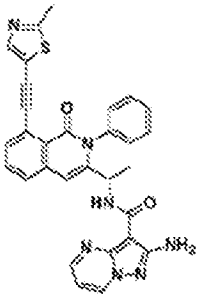
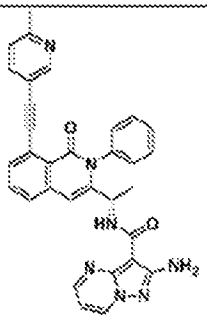
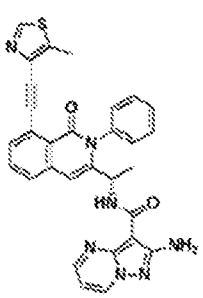
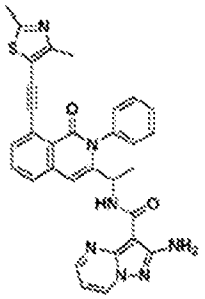
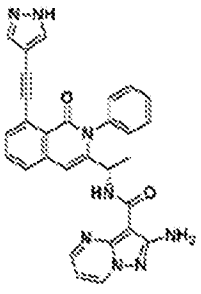
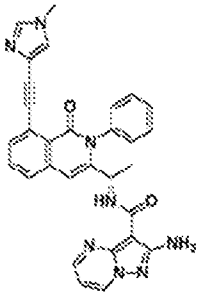
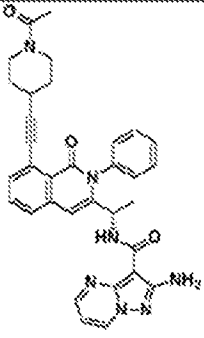
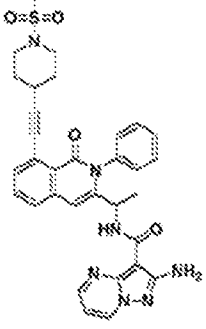


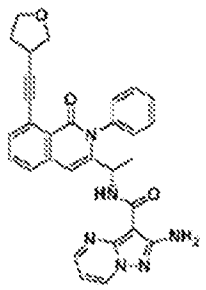
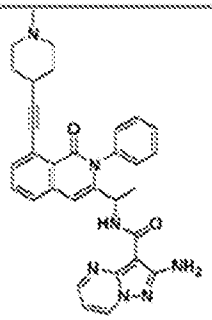
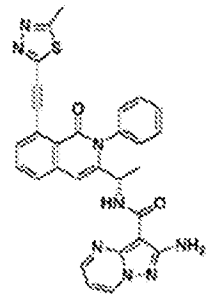
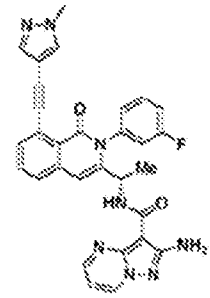
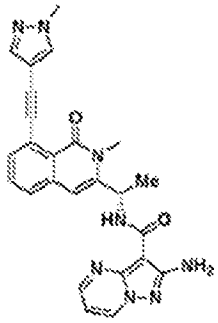
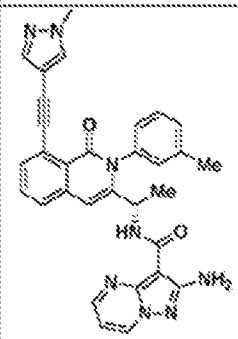
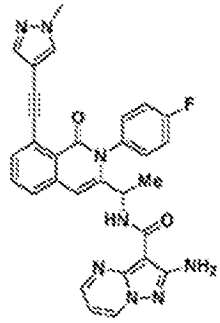
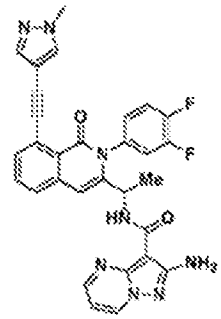
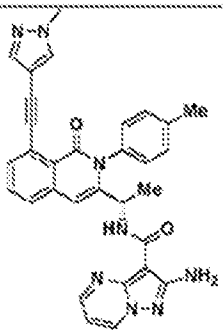
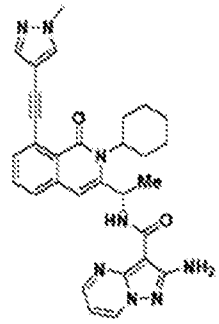
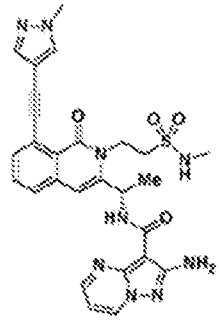
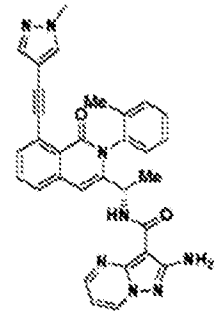
 Forbindelse 14,	 Forbindelse 15,	 Forbindelse 16,	 Forbindelse 17,
 Forbindelse 18,	 Forbindelse 19,	 Forbindelse 20,	 Forbindelse 22,
 Forbindelse 23,	 Forbindelse 24,	 Forbindelse 25,	 Forbindelse 26,

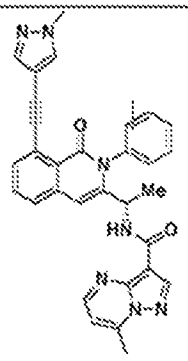
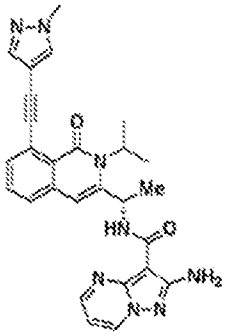
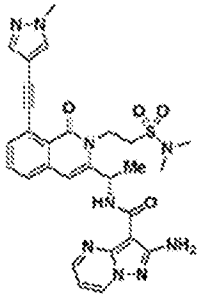
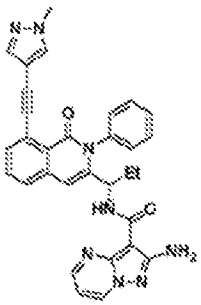
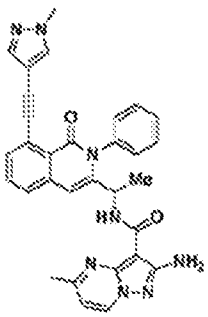
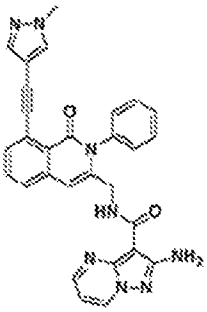
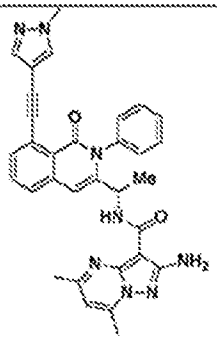
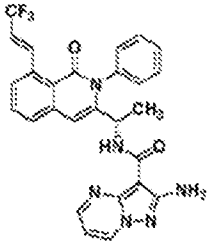
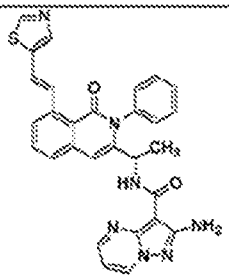
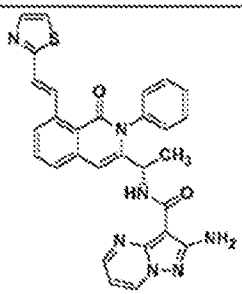
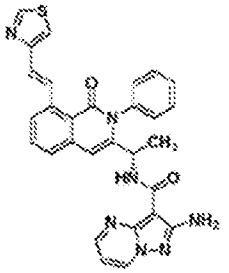
 Forbindelse 27.	 Forbindelse 28.	 Forbindelse 29.	 Forbindelse 30.
 Forbindelse 31.	 Forbindelse 32.	 Forbindelse 33.	 Forbindelse 34.
 Forbindelse 35.	 Forbindelse 36.	 Forbindelse 37.	 Forbindelse 38.

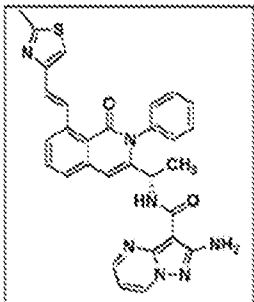
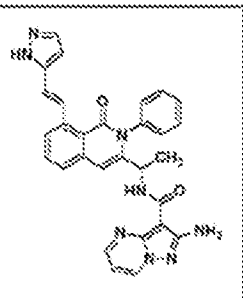
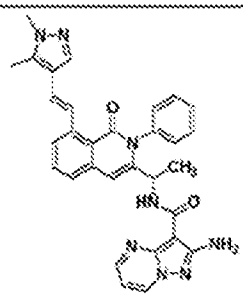
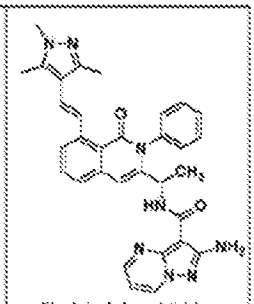
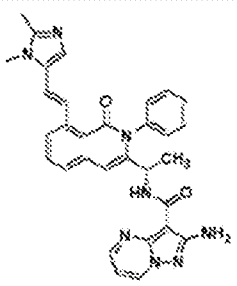
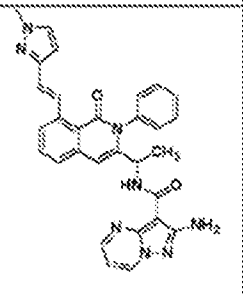
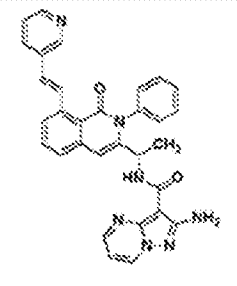
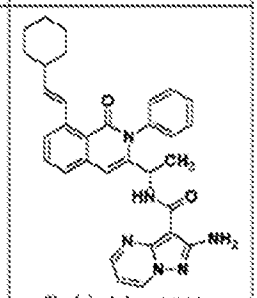
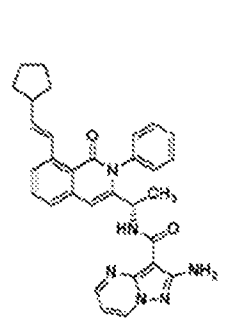
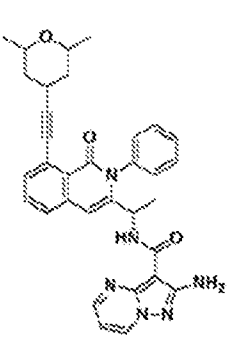
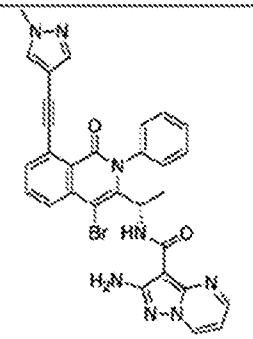
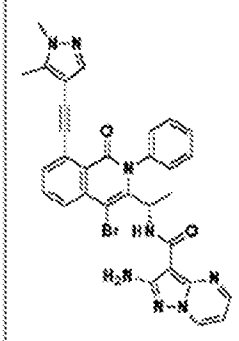
 Forbindelse 39.	 Forbindelse 40.	 Forbindelse 41.	 Forbindelse 42.
 Forbindelse 43.	 Forbindelse 44.	 Forbindelse 52.	 Forbindelse 53.
 Forbindelse 54.	 Forbindelse 56.	 Forbindelse 57.	 Forbindelse 58.

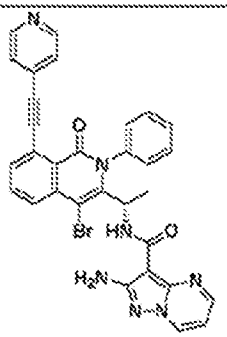
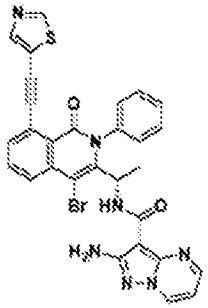
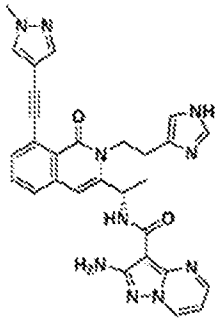
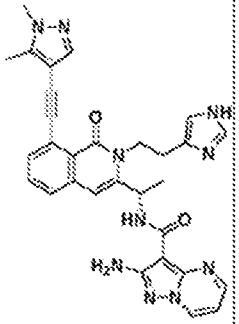
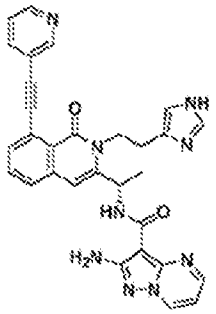
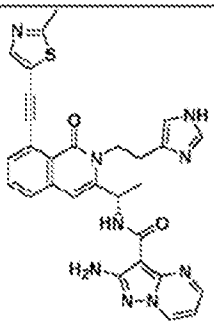
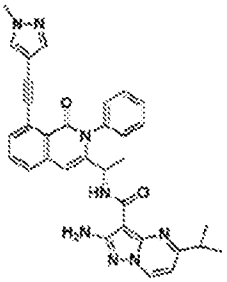
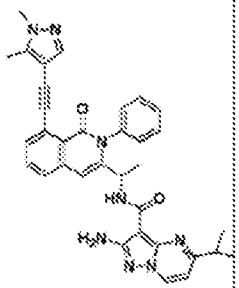
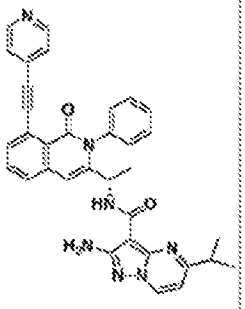
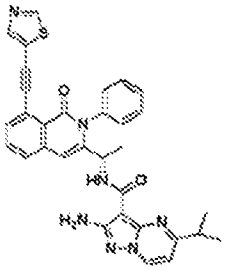
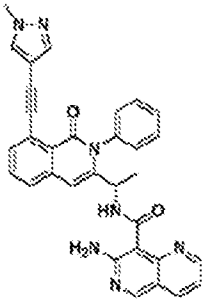
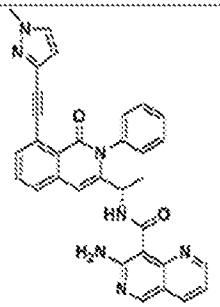
 Forbindelse 59.	 Forbindelse 60.	 Forbindelse 61.	 Forbindelse 62.
 Forbindelse 64.	 Forbindelse 65.	 Forbindelse 66.	 Forbindelse 67.
 Forbindelse 68.	 Forbindelse 69.	 Forbindelse 70.	 Forbindelse 71.

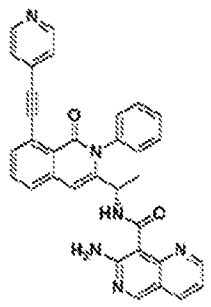
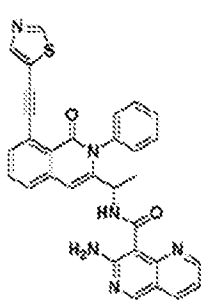
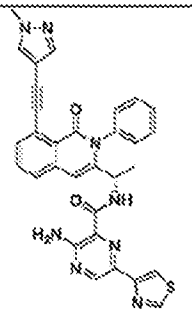
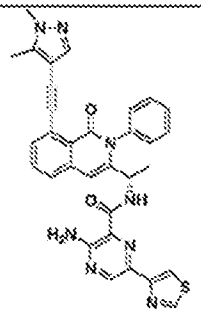
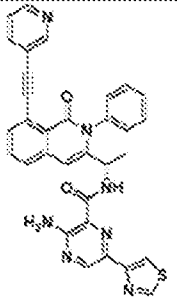
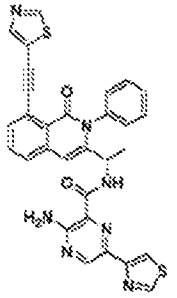
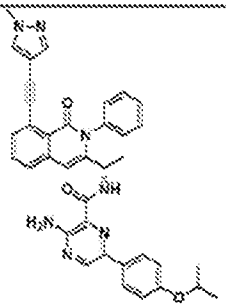
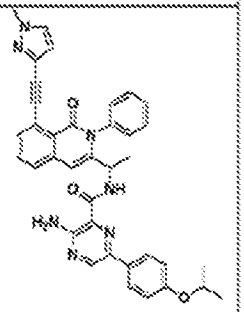
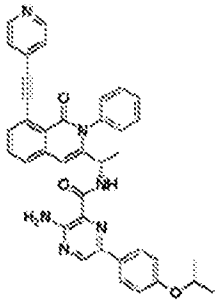
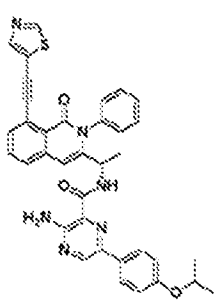
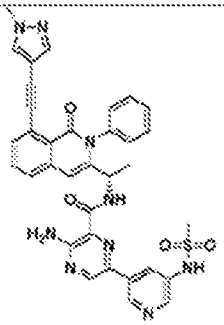
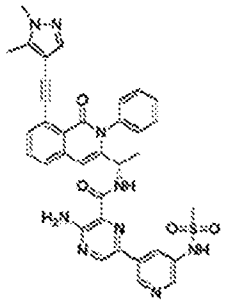
 Forbindelse 72.	 Forbindelse 73.	 Forbindelse 74.	 Forbindelse 75.
 Forbindelse 76.	 Forbindelse 77.	 Forbindelse 78.	 Forbindelse 79.
 Forbindelse 80.	 Forbindelse 81.	 Forbindelse 82.	 Forbindelse 83.

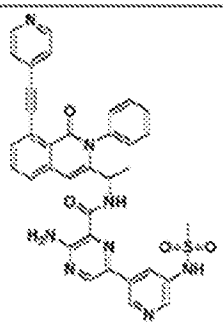
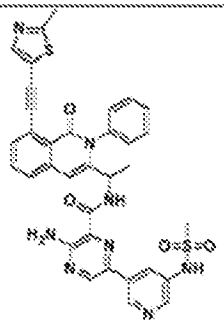
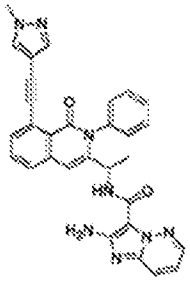
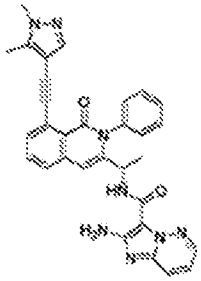
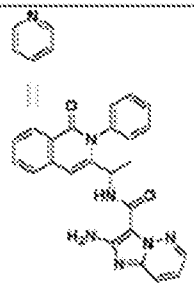
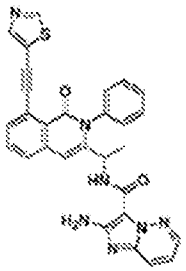
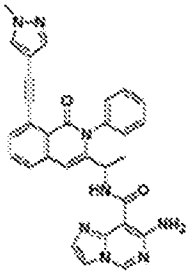
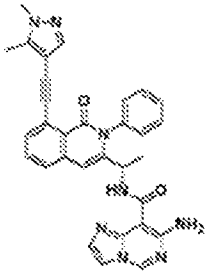
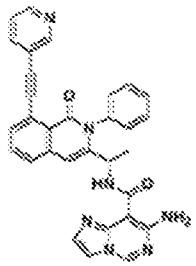
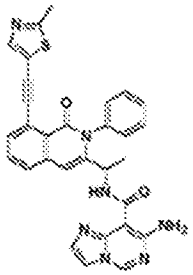
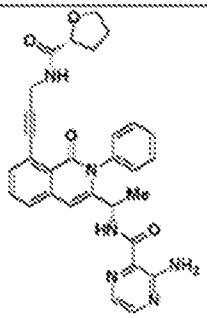
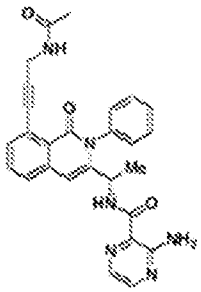
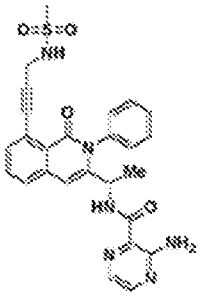
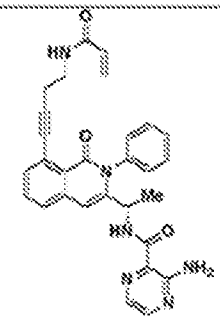
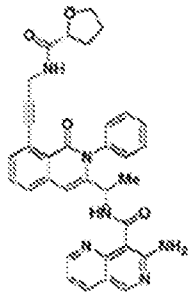
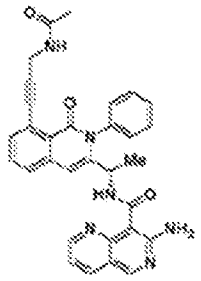
 Forbindelse 84.	 Forbindelse 85.	 Forbindelse 86.	 Forbindelse 93.
 Forbindelse 94.	 Forbindelse 95.	 Forbindelse 96.	 Forbindelse 97.
 Forbindelse 98.	 Forbindelse 99.	 Forbindelse 100.	 Forbindelse 101.

 Forbindelse 102,	 Forbindelse 103,	 Forbindelse 104,	 Forbindelse 105,
 Forbindelse 106,	 Forbindelse 107,	 Forbindelse 108,	
 Forbindelse 1001,	 Forbindelse 1002,	 Forbindelse 1003,	 Forbindelse 1004,

 Forbindelse 1005.	 Forbindelse 1006.	 Forbindelse 1007.	 Forbindelse 1008.
 Forbindelse 1009.	 Forbindelse 1010.	 Forbindelse 1011.	 Forbindelse 1012.
 Forbindelse 1013.	 Forbindelse 1014.	 Forbindelse 1041.	 Forbindelse 1042.

 Forbindelse 1043,	 Forbindelse 1044,	 Forbindelse 1045,	 Forbindelse 1046,
 Forbindelse 1047,	 Forbindelse 1048,	 Forbindelse 1049,	 Forbindelse 1050,
 Forbindelse 1051,	 Forbindelse 1052,	 Forbindelse 1053,	 Forbindelse 1054,

 Forbindelse 1055,	 Forbindelse 1056,	 Forbindelse 1057,	 Forbindelse 1058,
 Forbindelse 1059,	 Forbindelse 1060,	 Forbindelse 1061,	 Forbindelse 1062,
 Forbindelse 1063,	 Forbindelse 1064,	 Forbindelse 1065,	 Forbindelse 1066,

 Forbindelse 1067.	 Forbindelse 1068.	 Forbindelse 1069.	 Forbindelse 1070.
 Forbindelse 1071.	 Forbindelse 1072.	 Forbindelse 1073.	 Forbindelse 1074.
 Forbindelse 1075.	 Forbindelse 1076.	 Forbindelse 1077.	 Forbindelse 1078.
			

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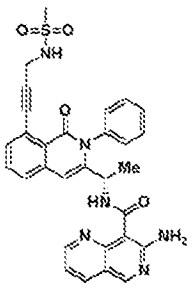	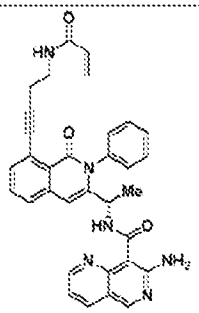	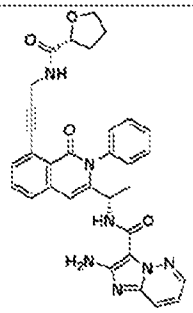	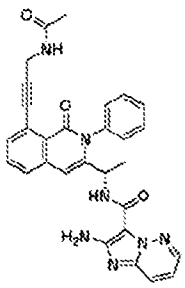
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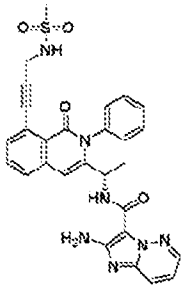	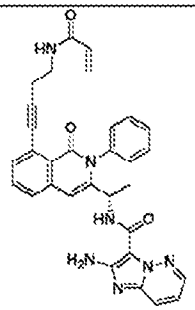	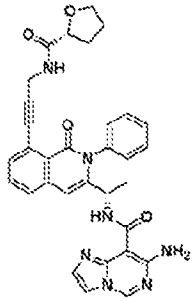	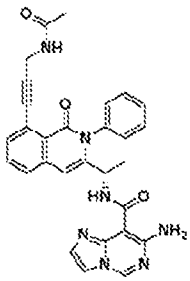
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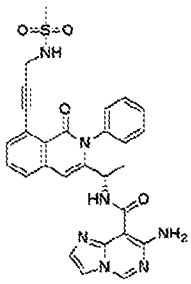
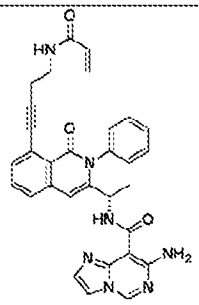
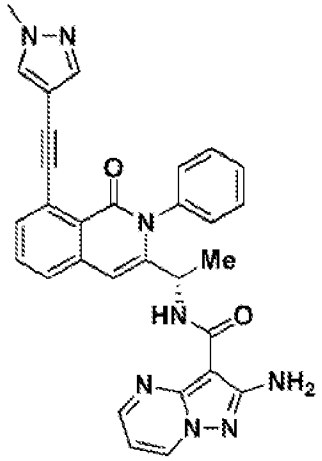
			
Forbindelse 1091 eller	Forbindelse 1092,		

eller et farmaceutisk acceptabelt salt deraf.

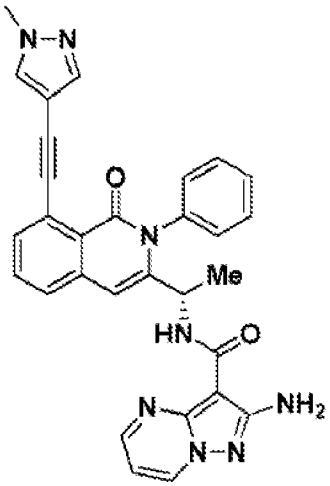
18. Forbindelse ifølge krav 1, som er:



Forbindelse 4,

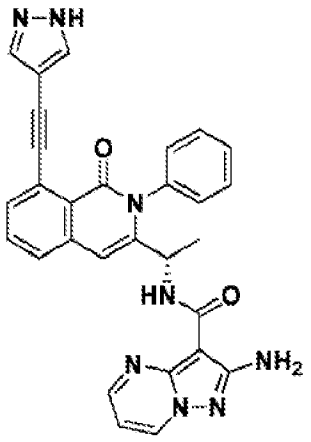
eller et farmaceutisk acceptabelt salt deraf.

19. Forbindelse ifølge krav 1, som er:



Forbindelse 4.

20. Forbindelse ifølge krav 1, som er:



Forbindelse 80,

eller et farmaceutisk acceptabelt salt deraf.

21. Farmaceutisk sammensætning omfattende en forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20, og et farmaceutisk acceptabelt hjælpestof, fortyndingsmiddel eller bærestof.

22. Farmaceutisk sammensætning omfattende en forbindelse eller farmaceutisk acceptabel form deraf ifølge krav 18, og et farmaceutisk acceptabelt hjælpestof, fortyndingsmiddel eller bærestof.

23. Farmaceutisk sammensætning omfattende en terapeutisk virksom mængde af en forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 og en PI3K-delta-hæmmer, fortrinsvis en PI3K-delta selektiv inhibitor, GS-1101 (Cal-101) eller AMG319.

24. En forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse til behandling af cancer; især en hæmatologisk cancer; f.eks. leukæmi eller lymfom, eller akut lymfocytisk leukæmi (ALL), kronisk lymfocytisk leukæmi (CLL), prolymfocytisk leukæmi (PLL), hårcelleleukæmi (HLL), Waldenstroms makroglobulinæmi (WM), perifere T-celle-lymfomer (PTCL), voksen-T-celle-leukæmi/lymfom (CTCL), kutant T-celle-lymfom (CTCL), storcellet granulær lymfocytisk

leukæmi (LGL), akut myelocytisk leukæmi (AML), Hodgkins lymfom (HL), ikke-Hodgkins lymfom (NHL), follikulært lymfom, diffust storcellet B-celle-lymfom (DLBCL), kappecelle-lymfom (MCL), mastocytose, multipelt myelom (MM), myelodysplastisk syndrom (MDS) eller myeloproliferativ lidelse (MPD).

25. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ved behandling af en fast solid tumor.

26. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ved behandling af cancer; især en hjernecancer, en hudcancer, hoved- og halscancer, eller en neuroendokrin cancer; en pankreatisk cancer, en lungecancer, en brystcancer, en prostatacancer, en testikelcancer, en øsofaguscancer, en levercancer, en gastrisk cancer, en tarmcancer, en kolorektal cancer, en æggestokcancer, en livmoderhalscancer, en uteruscancer, en endometriecancer, en blærecancer, en nyrecancer eller en virusinduceret cancer.

27. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ved behandling af en æggestokcancer.

28. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ved behandling af cancer; især en medulloblastom, en basal cellekarcinom, en gliom, en hepatocellulær cancer, en gastrointestinal stromal tumor (GIST), en melanom, en primitiv neuroektodermal tumor (PNT), en blødvævssarkom, fibrosarkoma, myxosarkom, liposarkom, en kondrosarkom, en osteosarkom, en chordom, en angiosarkom, en endotheliosarkom, en lymphangiosarkom, en lymphangioendotheliosarkom, en synoviom, en mesotheliom, en leiomyosarkom, en overgangscelle-karcinom i urinblæren, en epitelkarcinom, en pladecellekarcinom, en adenokarcinom, en bronchogen karcinom, en nyrecellekarcinom, en malign hepatom, en karcinoid tumor eller glioblastom.

29. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ved behandling af en melanom.

30. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ved behandling af en urothelial karcinom.

31. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ved behandling af en overgangscelle-karcinom i urinblæren.

32. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ved behandling af en nyrecelle-karcinom.

33. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ved behandling af en fast tumor; især melanom, lungecancer, hoved- og halscancer, nyrecelle-karcinom, blærecancer, brystcancer, tarmcancer, glioblastom, binyrecancer, mesotheliom, kolorektal cancer, æggestokcancer eller endometriecancer.

34. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ifølge krav 33, hvor den faste tumor er lungecancer, f.eks. småcellet cellelungecancer.

35. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ifølge krav 33, hvor den faste tumor er hoved- og halscancer, f.eks. hoved- og hals-pladecellekarcinom.

36. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ifølge krav 33, hvor den faste tumor er brystcancer.

37. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ifølge et af kravene 24-36, hvor canceren er metastatisk.

38. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ifølge et af kravene 24-36, hvor canceren er recidiv efter, eller refraktær over for, en forudgående terapi.

39. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ved behandling af en knoglelidelse, især en knoglelidelse, som resulterer af en ødelæggelse af en funktion af en osteoklast.

40. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af krav 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ved behandling af en luftvejssygdom; især en luftvejssygdom udvalgt blandt astma, cystisk fibrose, emfysem, kronisk obstruktiv lungesygdom (COPD), kronisk bronkitis, akut respiratorisk distress-syndrom, sygdomme i luftvejene, sygdomme i pleurale hulrum og pulmonær hypertension.

41. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af krav 1-20 eller en sammensætning ifølge krav 21 or 22 til anvendelse ved behandling af en inflammatorisk sygdom eller en autoimmun sygdom, især arthritis.

42. En forbindelse eller farmaceutisk acceptabel form deraf ifølge et af krav 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ifølge et af kravene 24-41, hvor forbindelsen, den farmaceutisk acceptable form eller sammensætning er til indgivelse i en mængde på ca. 0,1 mg til ca. 100 mg pr. dag, ca. 1 mg til 50 mg pr. dag, ca. 5 mg til 40 mg pr. dag eller ca. 10 mg til 30 mg pr. dag.

43. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ifølge et af kravene 24-41, hvor forbindelsen eller det farmaceutisk acceptable salt deraf er til indgivelse i en mængde på ca. 5 mg til 40 mg pr. dag.

44. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ifølge et af kravene 24-41, hvor forbindelsen eller det farmaceutisk acceptable salt deraf er til indgivelse i en mængde på ca. 10 mg til 30 mg pr. dag.

45. En forbindelse eller farmaceutisk acceptabel form deraf ifølge et af kravene 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ifølge et af

kravene 24-41, hvor forbindelsen, den farmaceutisk acceptable form eller sammensætning er til indgivelse hver anden dag, en gang om dagen eller to gange om dagen.

46. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ifølge et af kravene 24-41, hvor forbindelsen, eller det farmaceutisk acceptable salt deraf, er til indgivelse en gang pr. dag.

47. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af krav 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ifølge et af kravene 24-46, hvor forbindelsen, den farmaceutisk acceptable form eller sammensætning er til indgivelse oralt eller ved inhalation.

48. Forbindelse eller farmaceutisk acceptabel form deraf ifølge et af krav 1-20 eller en sammensætning ifølge krav 21 eller 22 til anvendelse ifølge et af kravene 24-47, hvor forbindelsen eller sammensætningen er til indgivelse i kombination med et eller flere andre terapeutiske midler; fortrinsvis Norvir (ritonavir); en PI3K-delta-hæmmer, mere fortrinsvis en PI3K-delta selektiv hæmmer, GS-1101 (Cal-101) eller AMG319; eller en mTOR-hæmmer; eller en costimulatorisk modulator, en immunostimulant eller en CXCL12/CXCR4-hæmmer; en HDAC-hæmmer, en proteasom-hæmmer, et CD28-antistof, et CD30-antistof eller et CD40-antistof; GM-CSF; eller gemcitabin, cyclophosphamid, docetaxel, paclitaxel, 5-FU eller temozolomid; eller en anden terapi, fortrinsvis en stråleterapi, hvor forbindelsen, den farmaceutisk acceptable form eller sammensætning fortrinsvis indgives efter, samtidig med eller alene efter at have afbrudt stråleterapien.

49. Forbindelse, eller farmaceutisk acceptabelt salt deraf, ifølge krav 18, til anvendelse ifølge et af kravene 24, 26, 28, 33, hvor forbindelsen eller det farmaceutiske acceptable salt deraf, er til indgivelse i kombination med paclitaxel.