HETEROAROMATIC COMPOUNDS AS PI3 KINASE MODULATORS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims the benefit of U.S. Provisional Application Serial Number 61/726,139, filed on November 14, 2012, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[002] The invention disclosed herein relates to the field of protein kinases and inhibitors thereof. In particular, the invention relates to modulators of phosphatidylinositol 3-kinases (PI3 kinases or PI3Ks) signaling pathways, and methods of use thereof.

BACKGROUNDOF THE INVENTION

[003] The phosphoinositide 3-kinases (PI3 kinases or PI3Ks), a family of lipid kinases, have been found to have key regulatory roles in many cellular processes including cell survival, proliferation and differentiation. As major effectors downstream of receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs), PI3Ks transduce signals from various growth factors and cytokines into intracellular massages by generating phospholipids, which activate the serine-threonine protein kinase AKT (also known as protein kinase B (PKB)) and other downstream effector pathways. The tumor suppressor or PTEN (phosphatase and tensin homologue) is the most important negative regulator of the PI3K signaling pathway ("Small-molecule inhibitors of the PI3K signaling network." Future Med. Chem., 2011, 3(5), 549-565).

[004] The phosphoinositide 3-kinase (PI3K) pathway is an important signal transduction pathway commonly activated in cancer. Activated PI3K pathway leads to phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5 -trisphosphate (PIP3). PIP3 can be dephosphorylated by the phosphatase and tensin homolog (PTEN), which terminates PI3K signaling. The accumulation of PIP3 activates a signaling cascade starting with the phosphorylation (activation) of the protein serine-threonine kinase AKT

at threonine 308 by phosphoinositide-dependent kinase 1 (PDK1). Phosphotylated AKT activates the mammalian target of rapamycin (mTOR), which leads to phosphorylation of its downstream targets.

[005] There are three PI3K classes, with different structures and characteristics; class I can be further subdivided into class Ia and class Ib. Class II PI3Ks are large (170-210 kDa) proteins that have a catalytic domains that mediate calicium/lipid binding in classical protein kinase C isoforms. Class III PI3Ks are typified by the yeast protein encoded by the VPS34 gene and phosphorylate only PtdIns to produce PtdIns(3)P; they are thought to regulate vesicle transport (Targeting PI3K signaling in cancer: opportunities, challenges and limitations." Nature Review Cancer, 2009, 9, 550).

[006] Class Ia PI3Ks (PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ) comprises heterodimers between a p110 catalytic subunit (p110α, p110β, p110γ and p110δ respectively), and a p85 regulatory adapter subunits (i.e., p85α, p85β, p55δ, p55α and p50α). The catalytic p110 subunit uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. The importance of Class Ia PI3Ks in cancer was confirmed by the discovery that the PI3K catalytic subunit α-isoform gene (PIK3CA), which encodes p110α, is frequently mutated or amplified in a number of human tumors such as ovarian cancer (Campbell et al, Cancer Res 2004, 64, 7678-7681 ; Levine et al., Clin Cancer Res 2005, 11, 2875-2878; Wang et al., Hum Mutat 2005, 25, 322; Lee et al., Gynecol Oncol 2005, 97, 26-34), cervical cancer, breast cancer (Bachman, et al. Cancer Biol Ther 2004, 3, 772-775; Levine, et al., supra; Li et al., Breast Cancer Res Treat 2006, 96, 91-95; Saal et al., Cancer Res 2005, 65, 2554-2559; Samuels and Velculescu, Cell Cycle 2004, 3, 1221-1224), colorectal cancer (Samuels, et al. Science 2004, 304, 554; Velho et al. Eur J Cancer 2005, 41, 1649-1654), endometrial cancer (Oda et al. Cancer Res. 2005, 65, 10669-10673), gastric carcinomas (Byun et al., M J Cancer 2003, 104, 318-327; Li et al., supra; Velho et al., supra; Lee et al., Oncogene 2005, 24, 1477-1480), hepatocellular carcinoma (Lee et al., id), small and non-small cell lung cancer (Tang et al., Lung Cancer 2006, Jl, 181-191; Massion et al., Am J Respir Crit Care Meaf 2004, 1 70, 1088-1094), thyroid carcinoma (Wu et al, J Clin Endocrinol Metαb 2005, 90, 4688-4693), acute myelogenous leukemia (AML) (Sujobert et al., Blood 1997, 106, 1063-1066), chronic myelogenous leukemia (CML) (Hickey and Cotter J Biol Chem 2006, 281, 2441-2450), and glioblastomas (Hartmann et al. Acta Neuropαthol (Berl) 2005,

109, 639-642; Samuels et al., supra).

[007] mTOR is a highly conserved serine-threonine kinase with lipid kinase activity and participitates as an effector in the PI3K/AKT pathway. mTOR exists in two distinct complexes, mTORC1 and mTORC2, and plays an important role in cell proliferation by monitoring nutrient avaliability and cellular energy levels. The downstream targets of mTORC1 are ribosomal protein S6 kinase 1 and eukaryotic translation initiation factor 4E-binding protein 1, both of which are crucial to the regulation of protein synthesis. ("Present and future of PI3K pathway inhibition in cancer: perspectives and limitations." Current Med. Chem. 2011, 18, 2647-2685).

[008] Knowledge about consequences of dysregulated mTOR signaling for tumorigenesis comes mostly from studies of pharmacologically disruption of mTOR by repamycin and its analogues such as temsirolimus (CCI-779) and everolimus (RAD001). Rapamycin was found to inhibit mTOR and thereby induce G1 arrest and apoptosis. The mechanism of rapamycin growth inhibition was found to be related to formation of complexes of rapamycin with FK-binding protein 12 (FKBP-12). These complexes then bound with high affinity to mTOR, preventing activation and resulting in inhibition of protein translation and cell growth. Cellular effects of mTOR inhibition are even more pronounced in cells that have concomitant inactivation of PTEN. Antitumor activity of rapamycin was subsequently identified, and a number of rapamycin analogues such as temsirolimus and everolimus have been approved by the US Food and Drug Adminstration for the treatment certain types of cancer.

[009] In view of the important role of PI3Ks amd mTOR in biological processes and disease states, inhibitors of these kinases are desirable ("Phosphatidylinositol 3-kinase isoforms asa novel drug targets." Current Drug Targets, 2011, 12, 1056-1081; "Progress in the preclinical discovry and clinical development of class I and dual class I/IV phosphoinositide 3-kinase (PI3K) inhibitors." Current Med Chem 2011, 18, 2686-2714).

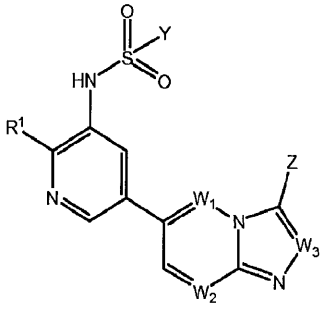
SUMMARY OF THE INVENTION

[010] The following only summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All references cited in this specification are hereby incorporated by reference in their entirety. In the event of a discrepancy between the express disclosure of this specification

and the references incorporated by reference, the express disclosure of this specification shall control.

[011] Provided herein are compounds that inhibit, regulate, and/or modulate PI3K and/or mTOR, and are useful in the treatment of hyperproliferative diseases, such as cancer, in humans. Also provided herein are methods of making the compound, methods of using such compounds in the treatment of hyperproliferative diseases in humans and pharmaceutical compositions containing such compounds.

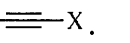
[012] The first aspect of the invention provides a compound of Formula (I):



(I),

or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a solvate, a metabolite, a pharmaceutically salt or a prodrug thereof, wherein each of Y, Z, R^1, W_1, W_2 and W_3 is as defined herein.

[013] In certain embodiments, each of W_1, W_2 and W_3 is independently N or CR^c;

Z is D, CN, N_3 or ;

X is H, D, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(C_1$-$C_4)$alkylene-CN, -$(C_1$-$C_4)$alkylene-OR^a, -$(C_1$-$C_4)$alkylene-NR^aR^b, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl;

Y is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, -$(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_6)$cycloalkyl, -$(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_6)$heterocyclyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, -$(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_6)$cycloalkyl, -$(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_6)$heterocyclyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, -$(C_1\text{-}C_4)$alkylene-CN, -$(C_1\text{-}C_4)$alkylene-OR^a, -$(C_1\text{-}C_4)$alkylene-NR^aR^b, $(C_6\text{-}C_{10})$aryl and 5-10 membered heteroaryl;

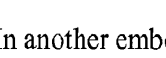
R^1 is H, D, Cl, OR^a, NR^aR^b, $(C_1\text{-}C_6)$aliphatic or $(C_3\text{-}C_6)$cycloalkyl, wherein each of the $(C_1\text{-}C_6)$aliphatic and $(C_3\text{-}C_6)$cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OR^a, SR^a and NR^aR^b, provided that when each of W_1, W_2 and W_3 is CH, R^1 is not H or NH_2;

each R^a and R^b is independently H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, -$(C_1\text{-}C_4)$alkylene-$(C_6\text{-}C_{10})$aryl or -$(C_1\text{-}C_4)$alkylene-(5-10 membered heteroaryl); or when R^a and R^b are bonded to the same nitrogen atom, R^a and R^b, together with the nitrogen atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered heterocyclic ring, wherein each of the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OH, NH_2, $(C_1\text{-}C_6)$alkoxy, and $(C_1\text{-}C_6)$alkylamino; and

each R^c is independently H, D, F, Cl, Br, I, N_3, CN, OH, NH_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylamino, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylamino, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OH, NH_2, $(C_1\text{-}C_6)$alkyl,

$(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy and $(C_1$-$C_6)$alkylamino.

[014] In another embodiment, each of W_1 and W_2 is independently N or CR^c, W_3 is CR^c.

[015] In another embodiment, Z is CN, N_3 or .

[016] In another embodiment, X is H, D, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl or -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl and -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl and $(C_2$-$C_6)$alkynyl.

[017] In another embodiment, Y is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl.

[018] In another embodiment, R^1 is H, D, Cl, CH_3, CH_2CH_3, CF_3, CH_2CF_3, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$, provided that when each of W_1, W_2 and W_3 is CH, R^1 is not H or NH_2.

[019] In another embodiment, each R^c is independently H, D, F, Cl, N_3, CN, NH_2, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylamino, $(C_3$-$C_6)$cycloalkyl or $(C_3$-$C_6)$heterocyclyl, wherein each of the $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylamino, $(C_3$-$C_6)$cycloalkyl and $(C_3$-$C_6)$heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, CN, N_3, OH, NH_2, $(C_1$-$C_3)$alkyl, $(C_3$-$C_6)$cycloalkyl and $(C_1$-$C_3)$haloalkyl.

[020] In another aspect, provided herein are pharmaceutical compositions comprising a compound disclosed herein, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, pharmaceutically acceptable salt or prodrug thereof, and an optional pharmaceutically acceptable

carrier, excipient, diluent, adjuvant, vehicle or a combination thereof. In certain embodiments, the compound is a modulator of PI3K.

[021] In some embodiments, the pharmaceutical composition disclosed herein further comprises an additional therapeutic agent. In other embodiments, the therapeutic agent is a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis or a combination thereof.

[022] In certain embodiments, the additional therapeutic agent is chlorambucil, melphalan, cyclophosphamide, ifosfamide, busulfan, carmustine, lomustine, streptozocin, cisplatin, carboplatin, oxaliplatin, dacarbazine, temozolomide, procarbazine, methotrexate, fluorouracil, cytarabine, gemcitabine, mercaptopurine, fludarabine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, topotecan, irinotecan, etoposide, trabectedin, dactinomycin, doxorubicin, epirubicin, daunorubicin, mitoxantrone, bleomycin, mitomycin, ixabepilone, tamoxifen, flutamide, gonadorelin analogues, megestrol, prednidone, dexamethasone, methylprednisolone, thalidomide, interferon alfa, leucovorin, sirolimus, temsirolimus, everolimus, afatinib, alisertib, amuvatinib, apatinib, axitinib, bortezomib, bosutinib, brivanib, cabozantinib, cediranib, crenolanib, crizotinib, dabrafenib, dacomitinib, danusertib, dasatinib, dovitinib, erlotinib, foretinib, ganetespib, gefitinib, ibrutinib, icotinib, imatinib, iniparib, lapatinib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, nilotinib, niraparib, oprozomib, olaparib, pazopanib, pictilisib, ponatinib, quizartinib, regorafenib, rigosertib, rucaparib, ruxolitinib, saracatinib, saridegib, sorafenib, sunitinib, tasocitinib, telatinib, tivantinib, tivozanib, tofacitinib, trametinib, vandetanib, veliparib, vemurafenib, vismodegib, volasertib, alemtuzumab, bevacizumab, brentuximab vedotin, catumaxomab, cetuximab, denosumab, gemtuzumab, ipilimumab, nimotuzumab, ofatumumab, panitumumab, ramucirumab, rituximab, tositumomab, trastuzumab, or a combination thereof.

[023] In another aspect, provided herein are methods for preventing, managing, treating or lessening the severity of a proliferative disorder in a patient infected with the proliferative disorder, which comprises administrating a pharmaceutically effective amount of the compound disclosed herein, or the pharmaceutical composition disclosed herein to the patient.

[024] In another aspect, provided herein is use of the compound disclosed herein, or the

pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening the severity of a proliferative disorder in a patient.

[025] In some embodiments, the proliferative disorder is metastatic cancer. In other embodiments, the proliferative disorder is colon cancer, gastric adenocarcinoma, bladder cancer, breast cancer, kidney cancer, liver cancer, lung cancer, skin cancer, thyroid cancer, cancer of the head and neck, prostate cancer, pancreatic cancer, cancer of the CNS, glioblastoma or a myeloproliferative disorder. In further embodiments, the proliferative disorder is atherosclerosis or lung fibrosis.

[026] In another aspect, provided hereinis a method of inhibiting or modulating PI3K and/or mTOR activity in a biological sample comprising contacting a biological sample with the compound disclosed herein, or the pharmaceutical composition disclosed herein.

[027] In some embodiments, provided herein is a method of inhibiting or modulating PI3K or mTOR, the method comprising contacting the kinase with the compound according to the present invention, or with the composition according to the present invention. In some embodiments, the invention provides a method of inhibiting or modulating PI3K or mTOR signaling, the method comprising contacting the receptor with the compound according to the present invention, or with the composition according to the present invention. In some embodiments, inhibition or modulation of PI3K or mTOR activity can be in a cell or a multicellular organism. If in a multicellular organism, the method according to this aspect of the invention comprises administering to the organism the compound according to the present invention, or the composition according to the present invention. In some embodiments, the organism is a mammal. In other embodiments is a human. In still other embodiment, the method further comprises contacting the kinase with an additional therapeutic agent.

[028] In another aspect, provided herein is a method of inhibiting proliferative activity of a cell, the method comprising contacting the cell with an effective proliferative inhibiting amount of a compound according to the present invention or a composition thereof. In some embodiments, the method further comprises contacting the cell with an additional therapeutic agent.

[029] In another aspect, provided herein is a method of treating a cell proliferative

disease in a patient, the method comprising administering to the patient in need of such treatment an effective therapeutic amount of the compound according to the present invention or the composition thereof. In some embodiments, the method further comprises administering an additional therapeutic agent.

[030] In some embodiments, provided herein is a method of inhibiting tumor growth in a patient, the method comprising administering to the patient in need thereof an effective therapeutic amount of the compound according to the present invention or the composition thereof. In some embodiments, the method further comprises administering an additional therapeutic agent.

[031] In another aspect, provided herein includes methods of preparing, methods of separating, and methods of purifying compounds of Formula (I).

[032] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS AND GENERAL TERMINOLOGY

[033] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. The invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described herein. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

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

[035] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in "Organic Chemistry" Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry" by Michael B. Smith and Jerry March, John Wiley & Sons, New York: 2007, the entire contents of which are hereby incorporated by reference.

[036] As used in the specification and claims, the term "a," "an," "the" and similar terms used in the context of the present invention are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[037] As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (e.g., humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[038] As used herein, "patient" refers to a human (including adults and children) or other animal. In one embodiment, "patient" refers to a human.

[039] The present invention also includes isotopically-labelled compounds, which are identical to those recited herein, but for the fact 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. Some non-limiting examples of isotopes that can be incorporated into the compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{36}S, ^{18}F, and ^{37}Cl.

[040] The compounds disclosed herein that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds disclosed herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain

therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

[041] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

[042] Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans- configuration.

[043] The compounds disclosed herein may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds disclosed herein, including but not limited to, diastereomers, enantiomers, atropisomers, and geometric (or conformational) isomers as well as mixtures thereof such as racemic mixtures, form part of the present invention.

[044] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, atropisomeric and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers.

[045] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. 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.

[046] Unless otherwise stated, all tautomeric forms of the compounds disclosed herein are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms.

[047] Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (R)-, (S)- or (R,S)-configuration. In certain embodiments, each asymmetric atom has at least 50% enantiomeric excess, at least 60% enantiomeric excess, at least 70% enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess in the (R)- or (S)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in cis- (Z)- or trans- (E)-form.

[048] Accordingly, as used herein a compound disclosed herein can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

[049] Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

[050] Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by methods known to those skilled in the art, e.g., by separation of the diastereomeric salts thereof. Racemic products can also be resolved by chiral chromatography, e.g., high performance liquid chromatography (HPLC) using a chiral adsorbent. Preferred enantiomers can also be prepared by asymmetric syntheses. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Principles of Asymmetric Synthesis (2nd Ed. Robert E. Gawley, Jeffrey Aubé, Elsevier, Oxford, UK, 2012); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[051] As described herein, the compounds disclosed herein may optionally be substituted with one or more substituents, such as are illustrated generally below, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted". In general, the term "substituted" whether proceeded by the term "optionally" or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. The term "optional" or "optionally" means that the subsequently described event or circumstance may but need notoccur, and that the description includes instances where the event or circumstance occurs and instances in which itdoes not. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position.

[052] The term "alkyl" or "alkyl group" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of 1 to 20 carbon atoms. Unless otherwise

specified, alkyl groups contain 1-20 carbon atoms. In some embodiments, alkyl groups contain 1-10 carbon atoms. In other embodiments, alkyl groups contain 1-8 carbon atoms. In still other embodiments, alkyl groups contain 1-6 carbon atoms. In yet other embodiments, alkyl groups contain 1-4 carbon atoms, and in further embodiments, alkyl groups contain 1-3 carbon atoms.

[053] Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl, 1-octyl, and the like. The alkyl radicals are optionally substituted independently with one or more substituents described herein.

[054] The terms "alkyl" and the prefix "alk-" as used herein, are inclusive of both straight chain and branched saturated carbon chain.

[055] The term "alkylene", as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, Unless otherwise specified, alkylene groups contain 1-6 carbon atoms. In some embodiments, alkylene groups contain 1-4 carbon atoms. In other embodiments, alkylene groups contain 1-2 carbon atoms. Alkylene group is exemplified by methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), isopropylene ($-CH(CH_3)CH_2-$), and the like.

[056] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted independently with one

or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Preferably, alkenyl group contains 2 to 8 carbon atoms, more preferably, 2 to 6 carbon atoms, and most preferably 2 to 4 carbon atoms. Examples include, but are not limited to, ethylenyl or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), and the like.

[057] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. Preferably, alkynyl group contains 2 to 8 carbon atoms, more preferably 2 to 6 carbon atoms, and most preferably 2 to 4 carbon atoms. Examples include, but are not limited to, ethynyl (-C≡CH), propynyl (propargyl, -CH_2C≡CH), -C≡C-CH_3, and the like.

[058] The term "aliphatic" or "aliphatic group" as used herein, refers to a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. In some embodiments, aliphatic groups contain 1-10 carbon atoms. In other embodiments, aliphatic groups contain 1-8 carbon atoms. In still other embodiments, aliphatic groups contain 1-6 carbon atoms. In yet other embodiments, aliphatic groups contain 1-4 carbon atoms, and in further embodiments, aliphatic groups contain 1-3 carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. For example, (C_1-C_6)aliphatic groups include unbranched or branched, unsubstituted or suitably substituted (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl groups. The aliphatic groups herein are optionally substituted independently with one or more substituents described herein.

[059] The term "alkoxy" as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon atom through an oxygen atom. Unless otherwise specified, alkoxy groups contain 1-20 carbon atoms. In some embodiments, alkoxy groups contain 1-10 carbon atoms. In other embodiments, alkoxy groups contain 1-8 carbon atoms. In still other embodiments, alkoxy groups contain 1-6 carbon atoms, and in yet other embodiments, alkoxy groups contain 1-3 carbon atoms.

[060] Examples of alkoxy groups include, but are not limited to, methoxy (MeO,

-OCH_3), ethoxy (EtO, -OCH_2CH_3), 1-propoxy (n-PrO, n-propoxy, -$OCH_2CH_2CH_3$), 2-propoxy (i-PrO, i-propoxy, -$OCH(CH_3)_2$), 1-butoxy (n-BuO, n-butoxy, -$OCH_2CH_2CH_2CH_3$), 2-methyl-l-propoxy (i-BuO, i-butoxy, -$OCH_2CH(CH_3)_2$), 2-butoxy (s-BuO, s-butoxy, -$OCH(CH_3)CH_2CH_3$), 2-methyl-2-propoxy (t-BuO, t-butoxy, -$OC(CH_3)_3$), 1-pentoxy (n-pentoxy, -$OCH_2CH_2CH_2CH_2CH_3$), 2-pentoxy (-$OCH(CH_3)CH_2CH_2CH_3$), 3-pentoxy (-$OCH(CH_2CH_3)_2$), 2-methyl-2-butoxy (-$OC(CH_3)_2CH_2CH_3$), 3-methyl-2-butoxy (-$OCH(CH_3)CH(CH_3)_2$), 3-methyl-l-butoxy (-$OCH_2CH_2CH(CH_3)_2$), 2-methyl-l-butoxy (-$OCH_2CH(CH_3)CH_2CH_3$), and the like. The alkoxy radicals are optionally substituted independently with one or more substituents described herein.

[061] The terms "haloalkyl" and "haloalkoxy" mean alkyl, or alkoxy, as the case may be, substituted with one or more halogen atoms.

[062] The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having 1 or 2 alkyl radicals of 1 to 6 carbon atoms attached to a nitrogen atom. Even more preferred alkylamino radicals contain 1 to 3 carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino, and the like.

[063] The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

[064] The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Some non-limiting examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl.

[065] The terms"carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloaliphatic" refer to a monovalent or multivalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system. A bicyclic ring system

includes a spiro bicyclyl or a fused bicyclyl. Suitable carbocyclyl groups include, but are not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl. Further non-limiting examples of carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-l-enyl, l-cyclopent-2-enyl, l-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-l-enyl, l-cyclohex-2-enyl, l-cyclohex-3-enyl, cyclohexadienyl, and the like.

[066] The term "cycloalkyl" refers to a monovalent or multivalent saturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system. A bicyclic ring system includes a spiro bicyclylor a fused bicyclyl. In some embodiments, a cycloalkyl contains 3 to 10 carbon atoms. In still other embodiments, a cycloalkyl contains 3 to 8 carbon atoms, and in yet other embodiments, a cycloalkyl contains 3 to 6 carbon atoms. The cycloalkyl radicals are optionally substituted independently with one or more substituents described herein.

[067] The term "heterocycle", "heterocyclyl" or "heterocyclic" as used interchangeably herein refers to a monocyclic, bicyclic, or tricyclic ring system in which one or more ring members are independently selected from heteroatoms and that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has one or more point of attachment to the rest of the molecule. A bicyclic ring system includes a spiro bicyclyl or a fused bicyclyl, and one of the rings can be either a monocarbocycle or a monohetercycle. One or more ring atoms are optionally substituted independently with one or more substituents described herein. In some embodiments, the "heterocycle", "heterocyclyl", or "heterocyclic" group is a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO_2, PO or PO_2). In other embodiments, it is a monocycle having 3 to 6 ring members (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO_2, PO or PO_2) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO_2, PO or PO_2).

[068] The heterocyclyl may be a carbon radical or heteroatom radical. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl,

tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homo-piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2*H*-pyranyl, 4*H*-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 1,2,3,4-tetrahydroisoquinolinyl. Some non-limiting examples of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidindionyl and 1, 1-dioxo-thiomorpholinyl.

[069] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon, including any oxidized form of nitrogen, sulfur, or phosphorus; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR (as in N- substituted pyrrolidinyl).

[070] The term "halogen" refers to fluoro (F), chloro (Cl), bromo (Br) or iodo (I).

[071] The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

[072] The term "D" or "^{2}H" denotes a single deuterium atom. One of this radical may be attached, for example, to a methyl group to form a mono-deuterated methyl group (-CDH_2), two of deuterium atoms may attached to a methyl group to form a di-deuterated methyl (-CD_2H), and three of deuterium atoms may attached to a methyl group to form a tri-deuterated methyl group (-CD_3).

[073] The term "N_3" denotes an azide moiety. This radical may be attached, for example, to a methyl group to form azidomethane (methyl azide, MeN_3); or attached to a phenyl group to form phenyl azide (PhN_3).

[074] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy" or "aryloxyalkyl" refers to monocyclic, bicyclic, and tricyclic carbocyclic ring systems having a total of 6 to 14 ring members, preferably, 6 to 12 ring members, and more preferably 6 to 10 ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3-7 ring members and that has one or more point of attachment to the rest of the

molecule. The term "aryl" may be used interchangeably with the term "aryl ring" or "aromatic". Some non-limiting examples of aryl rings would include phenyl, naphthyl, and anthracene. The aryl radicals are optionally substituted independently with one or more substituents described herein.

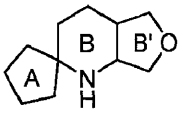
[075] The term "heteroaryl" used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy" refers to monocyclic, bicyclic, and tricyclic ring systems having a total of 5 to 14 ring members, preferably, 5 to 12 ring members, and more preferably 5 to 10 ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, wherein each ring in the system contains 5 to 7 ring members and that has a one or more point of attachment to the rest of the molecule. In some embodiments, a 5-10 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms independently selected from O, S and N. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic". The heteroaryl radicals are optionally substituted independently with one or more substituents described herein.

[076] Further non-limiting examples of heteroaryl rings include the following monocycles: 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5- tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5-triazinyl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), purinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl or 4-isoquinolinyl).

[077] The terms "fused bicyclic", "fused cyclic", "fused bicyclyl" and "fused cyclyl" are used interchangeably refer to a monovalent or multivalent saturated bridged ring system, which refers to a bicyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may

have aromatic substitution thereon).

[078] The terms "spirocyclyl", "spirocyclic", "spiro bicyclyl" or "spiro bicyclic" are used interchangeably and refer to a monovalent or multivalent ring system wherein a ring originating from a particular annular carbon of another ring. For example, as depicted below in Structure a, a saturated bridged ring system (ring B and B') is termed as "fused bicyclic", whereas ring A and ring B share an atom between the two saturated ring system, which terms as a "spirocyclyl" or "spiro bicyclyl". Each cyclic ring in a fused bicyclyl or a spiro bicyclyl can be either a carbocyclyl or a heterocyclyl.



Structure a

[079] The term "unsaturated" as used herein, means that a moiety has one or more units of unsaturation.

[080] The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

[081] The term "prodrug" as used herein, represents a compound that is transformed *in vivo* into a compound of formula (I). Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C_1-C_{24}) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compounddisclosed herein that contains an OH group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, for example those phosphates resulting from the phosphonation of an OH group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, J. Rautio et al, Prodrugs: Design and Clinical Applications, Nature Review Drug Discovery, 2008, 7, 255-270, and S. J. Hecker et al, Prodrugs of Phosphates and Phosphonates, Journal of Medicinal

Chemistry, 2008, 51, 2328-2345, each of which is incorporated herein by reference.

[082] A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of the compounds disclosed herein, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

[083] A "pharmaceutically acceptable salt" as used herein, refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* **1977**, 66, 1-19, which is incorporated herein by reference. Examples of pharmaceutically acceptable, nontoxic salts include, but are not limited to, 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, 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, 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. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization.

Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, 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, C_{1-8} sulfonate and aryl sulfonate.

[084] A "solvate" refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

[085] As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

[086] The term "a therapeutically effective amount" of a compound disclosed herein refers to an amount of the compound disclosed herein that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound disclosed herein that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by PI3K or (ii) associated with PI3K activity, or (iii) characterized by activity (normal or abnormal) of PI3K or (2) reduce or inhibit the activity of PI3K or (3) reduce or inhibit the expression of PI3K. In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound disclosed herein that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of PI3K; or at least partially

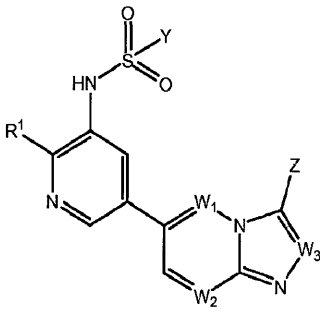
reducing or inhibiting the expression of PI3K. The meaning of the term "a therapeutically effective amount" as illustrated in the above embodiment for PI3K also applies by the same means to any other relevant proteins/peptides/enzymes.

[087] As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treat", "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

[088] The term "protecting group" or "PG" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting with other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC, Boc), benzyloxycarbonyl (CBZ, Cbz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl) ethoxy-methy-l, 2-(p-toluenesulfonyl) ethyl, 2-(p-nitrophenylsulfenyl)-ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley &Sons, New York, **1991** and P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, **2005**.

DESCRIPTION OF THE COMPOUNDS DISCLOSED HEREIN

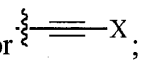
[089] Provided herein are heteroaromatic compounds, salts, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and disorders modulated by protein kinases, especially PI3K and mTOR. More specifically, the present invention provides a compound of Formula (I):



(I),

or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a solvate, a metabolite, a pharmaceutically salt or a prodrug thereof, wherein each of Y, Z, R^1, W_1, W_2 and W_3 is as defined herein.

[090] In certain embodiments, each of W_1, W_2 and W_3 is independently N or CR^c;

Z is D, CN, N_3 or ;

X is H, D, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, -C(=O)NR^aR^b, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(C_1$-$C_4)$alkylene-CN, -$(C_1$-$C_4)$alkylene-OR^a, -$(C_1$-$C_4)$alkylene-NR^aR^b, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl;

Y is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl,

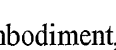
$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C_1$-$C_4)$alkylene-CN, $-(C_1$-$C_4)$alkylene-OR^a, $-(C_1$-$C_4)$alkylene-NR^aR^b, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl;

R^1 is H, D, Cl, OR^a, NR^aR^b, $(C_1$-$C_6)$aliphatic or $(C_3$-$C_6)$cycloalkyl, wherein each of the $(C_1$-$C_6)$aliphatic and $(C_3$-$C_6)$cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OR^a, SR^a and NR^aR^b, provided that when each of W_1, W_2 and W_3 is CH, R^1 is not H or NH_2;

each R^a and R^b is independently H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, $-(C_1$-$C_4)$alkylene-$(C_6$-$C_{10})$aryl or $-(C_1$-$C_4)$alkylene-(5-10 membered heteroaryl); or when R^a and R^b are bonded to the same nitrogen atom, R^a and R^b, together with the nitrogen atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered heterocyclic ring, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OH, NH_2, $(C_1$-$C_6)$alkoxy, and $(C_1$-$C_6)$alkylamino; and

each R^c is independently H, D, F, Cl, Br, I, N_3, CN, OH, NH_2, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OH, NH_2, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$alkoxy and $(C_1$-$C_6)$alkylamino.

[091] In another embodiment, each of W_1 and W_2 is independently N or CR^c, W_3 is CR^c.

[092] In another embodiment, Z is CN, N_3 or .

[093] In another embodiment, X is H, D, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl,

$(C_3$-$C_6)$heterocyclyl, $-(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl or $-(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, $-(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl and $-(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl and $(C_2$-$C_6)$alkynyl.

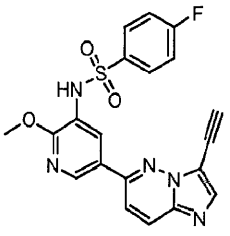
[094] In another embodiment, Y is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl.

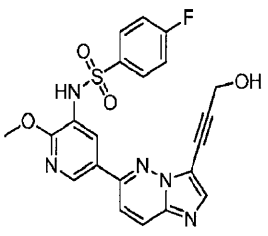
[095] In another embodiment, R^1 is H, D, Cl, CH_3, CH_2CH_3, CF_3, CH_2CF_3, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$, provided that when each of W_1, W_2 and W_3 is CH, R^1 is not H or NH_2.

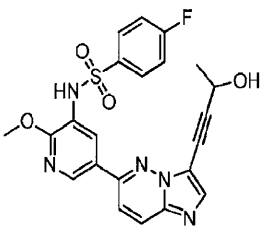
[096] In another embodiment, each R^c is independently H, D, F, Cl, N_3, CN, NH_2, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylamino, $(C_3$-$C_6)$cycloalkyl or $(C_3$-$C_6)$heterocyclyl, wherein each of the $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylamino, $(C_3$-$C_6)$cycloalkyl and $(C_3$-$C_6)$heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, CN, N_3, OH, NH_2, $(C_1$-$C_3)$alkyl, $(C_3$-$C_6)$cycloalkyl and $(C_1$-$C_3)$haloalkyl.

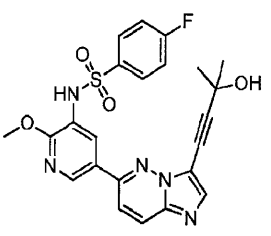
[097] Some non-limiting examples of the compounds disclosed hereinare shown in the following:

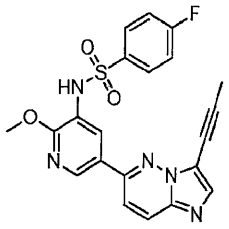
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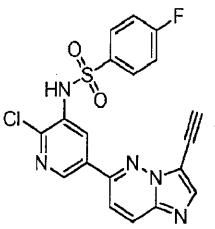

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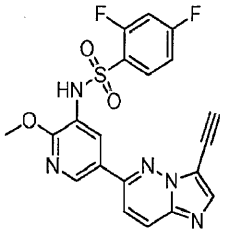

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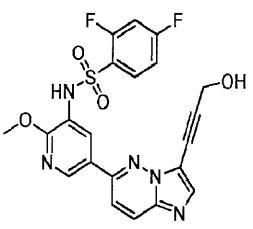

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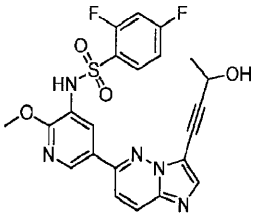

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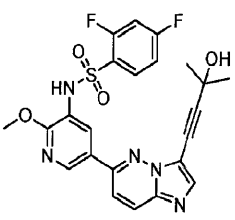

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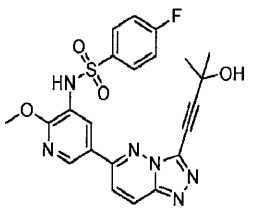

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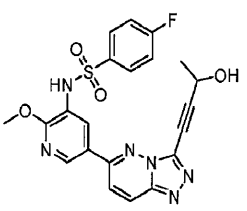

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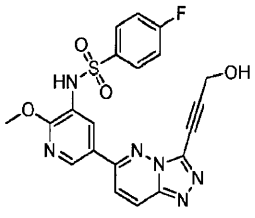

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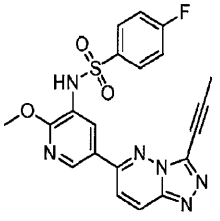

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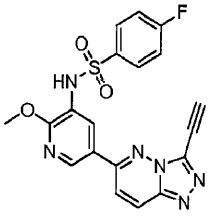

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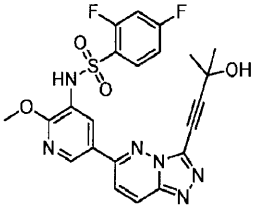

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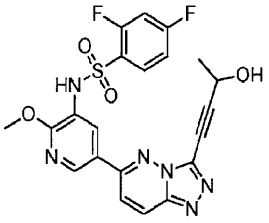

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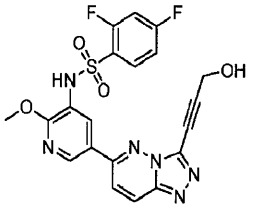

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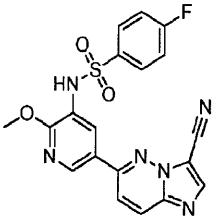

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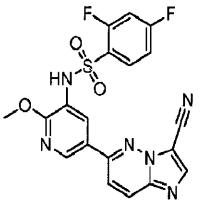

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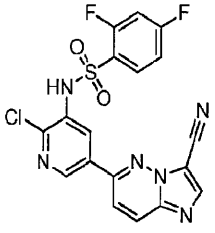

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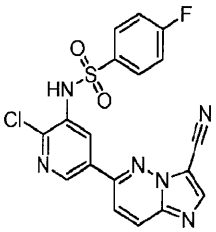

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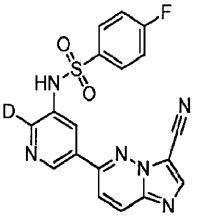

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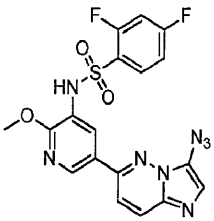

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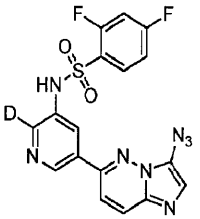

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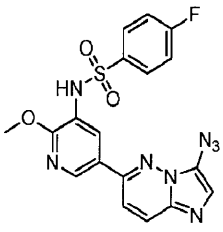

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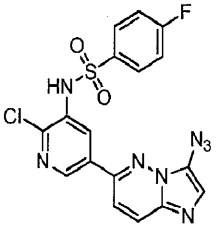

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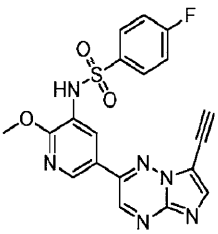

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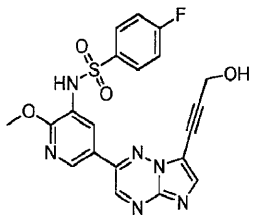

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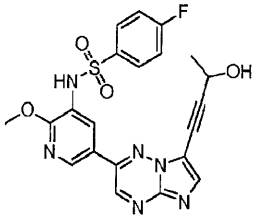

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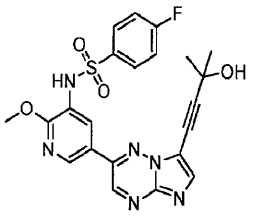

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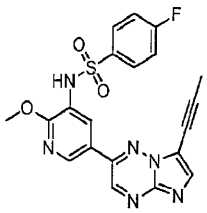

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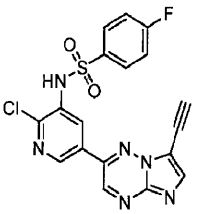

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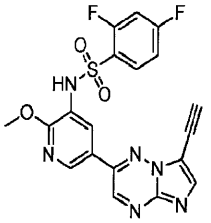

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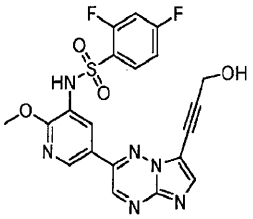

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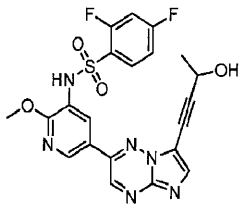

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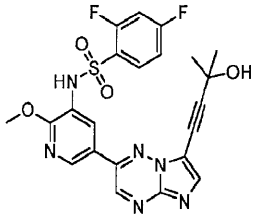

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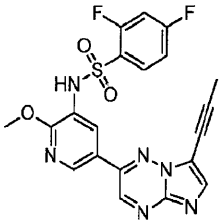

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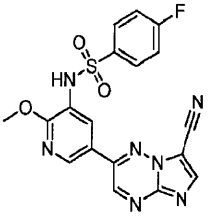

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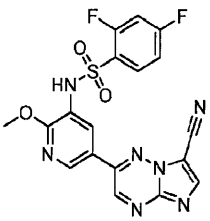

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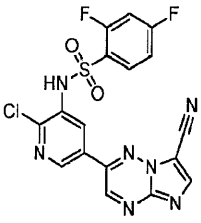

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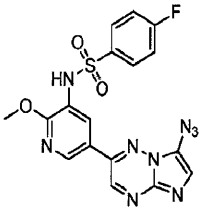

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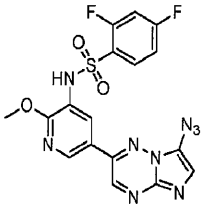

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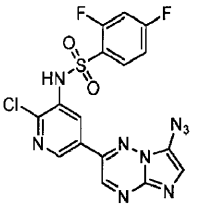

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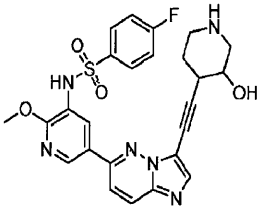

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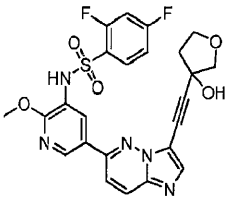

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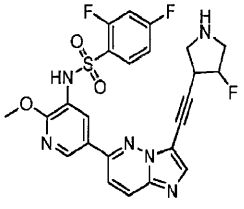

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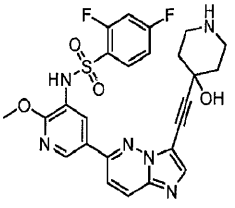

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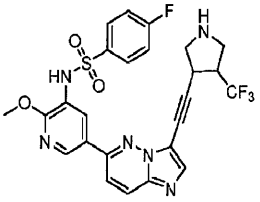

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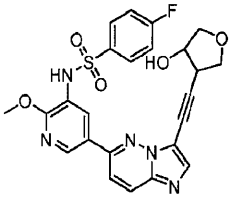

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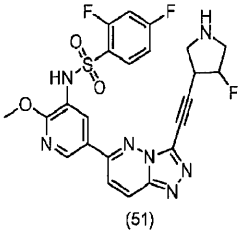

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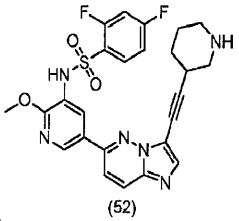

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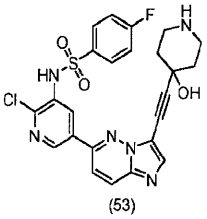

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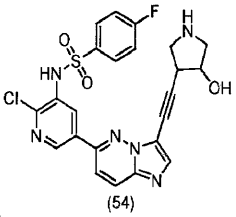

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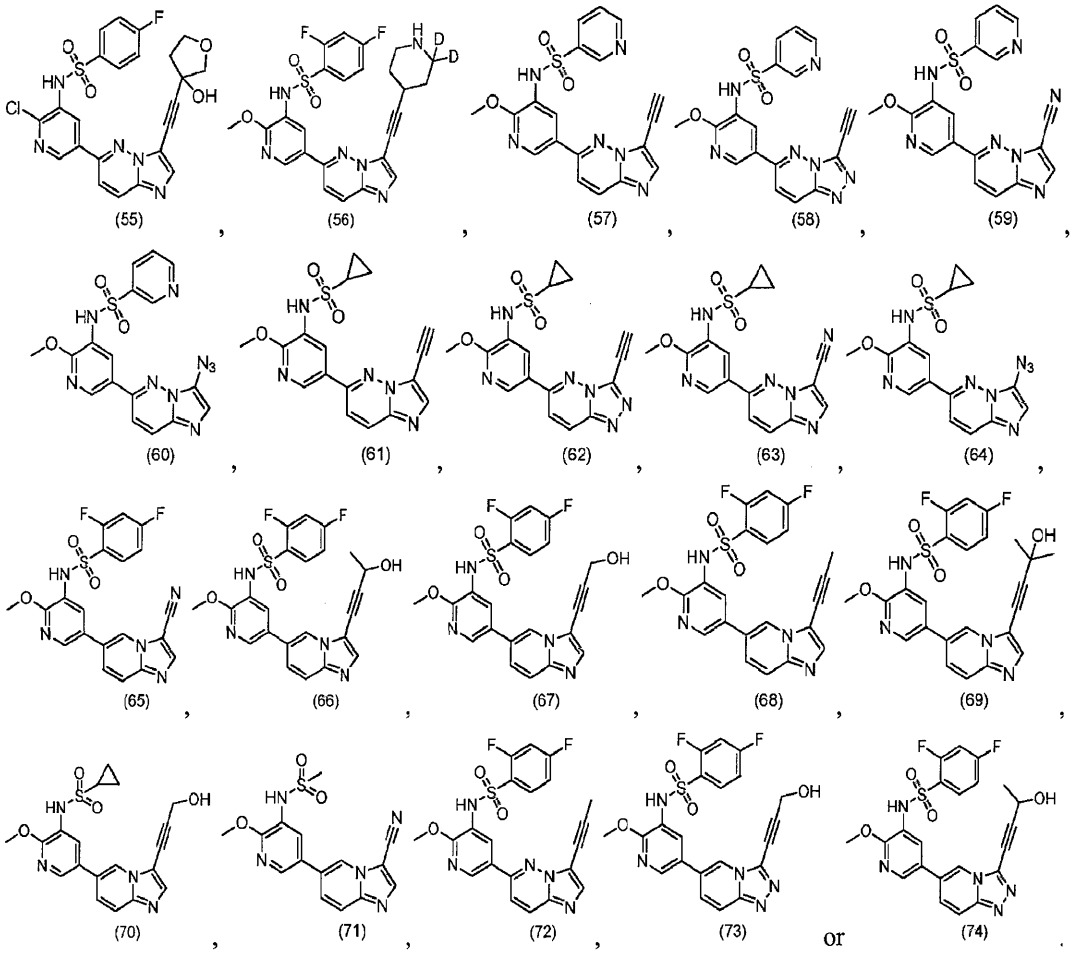

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[098] The present invention also comprises the use of a compound disclosed herein, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of a hyperproliferative disease state and/or an angiogenesis mediated disease state, including those described previously. The compounds disclosed herein are useful in the manufacture of an anti-cancer medicament. The compounds disclosed herein are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of protein kinases. The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) in association with at least one pharmaceutically acceptable carrier, adjuvant or diluent.

[099] The present invention also comprises a method of treating hyperproliferating and angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically effective amount of a compound of Formula (I).

[0100] Unless otherwise stated, all stereoisomers, geometric isomers, tautomers, solvates,

metabolites, salts, and pharmaceutically acceptable prodrugs of the compounds disclosed herein are within the scope of the invention.

[0101] In certain embodiments, the salt is a pharmaceutically acceptable salt. The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0102] The compounds disclosed hereinalso include salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula (I) and/or for separating enantiomers of compounds of Formula (I).

[0103] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, subsalicylate, tartrate, tosylate and trifluoroacetate salts.

[0104] Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[0105] Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

[0106] Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

[0107] Inorganic bases from which salts can be derived include, for example, ammonium

salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

[0108] 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. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[0109] The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[0110] Furthermore, the compounds disclosed herein, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds disclosed herein may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms.

[0111] In another aspect, provided herein are methods of preparing, methods of separating, and methods of purifying compounds of Formula (I). The compounds disclosed hereinmay have in general several asymmetric centers and are typically depicted in the form of racemic mixtures. This invention is intended to encompass racemic mixtures, partially racemic mixtures and separate enantiomers and diasteromers.

[0112] Compounds disclosed herein can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof. This invention is intended to encompass mixtures of isomers, rotamers, atropisomers, tautomers, partially mixed isomers, rotamers, atropisomers, or tautomers, and separated isomers, rotamers, atropisomers, tautomers.

[0113] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{36}S, ^{37}Cl, and ^{125}I respectively.

[0114] In another aspect, the compounds disclosed herein include isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{14}C and ^{18}F, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0115] Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein

means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, acetone-d_6, and DMSO-d_6.

COMPOSITION, FORMULATIONS AND ADMINSTRATION OF THE COMPOUNDS DISCLOSED HEREIN

[0116] According to one aspect, the invention features pharmaceutical compositions that include a compound of formula (I), a compound listed in Table 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in the compositions disclosed herein is such that is effective to detectably inhibit a protein kinase in a biological sample or in a patient.

[0117] It will also be appreciated that certain of the compounds disclosed herein can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0118] As described above, the pharmaceutically acceptable compositions disclosed herein invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage

form desired. In Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, are disclosed various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds disclosed 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, its use is contemplated to be within the scope of this invention.

[0119] Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0120] The compositions disclosed herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular,

intra-articular, intra-synovial, intrasternal, intrathecal, intraocular, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3- butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0121] For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0122] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0123] Alternatively, the pharmaceutically acceptable compositions of this invention may

be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0124] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the low intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0125] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used. For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0126] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated, e.g., as micronized suspensions in isotonic, pH adjusted sterile saline or other aqueous solution, or, preferably, as solutions in isotonic, pH adjusted sterile saline or other aqueous solution, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum. The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives,

absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0127] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0128] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0129] 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. In order to prolong the effect of a compound disclosed herein, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively,

dissolving or suspending the compound in an oil vehicle accomplishes delayed absorption of a parenterally administered compound form.

[0130] Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Some non-limitingexamples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0131] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non- irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0132] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0133] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high

molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Some non-limitingexamples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polythylene glycols and the like.

[0134] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain pacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Some non-limitingexamples of embedding compositions that can be used include polymeric substances and waxes.

[0135] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper

medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0136] The compounds disclosed herein are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions disclosed herein will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[0137] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 200 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0138] Compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other additional therapeutic (pharmaceutical) agents where the combination causes no unacceptable adverse effects. This may be of particular relevance for the treatment of hyper-proliferative diseases such as cancer. In this instance, the compound of this invention can be combined with known cytotoxic agents, signal transduction inhibitors, or with other anti-cancer agents, as well as with admixtures and combinations thereof. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated". As used herein, "additional therapeutic agents" is meant to include chemotherapeutic agents and other

anti-proliferative agents.

[0139] For example, chemotherapeutic agents or other antiproliferative agents may be combined with the compounds of this invention to treat proliferative disease or cancer. Examples of chemotherapeutic agents or other antiproliferative agents include HDAC inhibitors including, but are not limited to, SAHA, MS-275, MGO 103, and those described in WO 2006/010264, WO 03/024448, WO 2004/069823, US 2006/0058298, US 2005/0288282, WO 00/71703, WO 01/38322, WO 01/70675, WO 03/006652, WO 2004/035525, WO 2005/030705, WO 2005/092899, and demethylating agents including, but not limited to, 5-aza-dC, Vidaza and Decitabine and those described in US 6,268137, US 5,578,716, US 5,919,772, US 6,054,439, US 6,184,211, US 6,020,318, US 6,066,625, US 6,506,735, US 6,221,849, US 6,953,783, US 11/393,380.

[0140] In another embodiment of the present invention, for example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, for example, other therapies or anticancer agents that may be used in combination with the inventive anticancer agents of the present invention and include surgery, radiotherapy (in but a few examples, gamma radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, taxanes (paclitaxel, taxotere), platinum derivatives (cisplatin, carboplatin, oxaliplatin), biologic response modifiers (interferons, interleukins), tumor necrosis factor (TNF, TRAIL receptor targeting agents, to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (chlormethine, chlorambucil, cyclophosphamide, ifosfamide, melphalan, etc), anti-metabolites (methotrexate, raltitrexed, pemetrexed, etc), purine antagonists and pyrimidine antagonists (6-mercaptopurine, 5-fluorouracil, cytarabine, gemcitabine), spindle poisons (vinblastine, vincristine, vinorelbine), podophyllotoxins (etoposide, irinotecan, topotecan), antibiotics (doxorubicin, bleomycin, mitomycin), nitrosoureas (carmustine, lomustine), cell cycle inhibitors (KSP mitotic kinesin inhibitors, CENP-E and CDK inhibitors), enzymes (asparaginase), hormones (tamoxifen, leuprolide, flutamide, megestrol, dexamethasone), antiangiogenic agents (avastin and others),

monoclonal antibodies (Belimumab (BENLYSTA®), brentuximab (ADCETRIS®), cetuximab (ERBITUX®), gemtuzumab (MYLOTARG®), ipilimumab (YERVOY®), ofatumumab (ARZERRA®), panitumumab (VECTIBIX®), ranibizumab (LUCENTIS®), rituximab (RITUXAN®), tositumomab (BEXXAR®), trastuzumab (HERCEPTIN®), kinase inhibitors (imatinib (GLEEVEC®), sunitinib (SUTENT®), sorafenib (NEXAVAR®), cetuximab (ERBITUX®), trastuzumab (HERCEPTIN®), erlotinib (TARCEVA®), gefitinib (IRESSA®), dasatinib (SPRYCEL®), nilotinib (TASIGNA®), lapatinib (TYKERB®), crizotinib (XALKORI®), ruxolitinib (JAKAFI®), vemurafenib (ZELBORAF®), vandetanib (CAPRELSA®), pazopanib (VOTRIENT®), and others), and agents inhibiting or activating cancer pathways such as the mTOR, HIF (hypoxia induced factor) pathways (such as everolimus and temsirolimus) and others. For a more comprehensive discussion of updated cancer therapies see, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglist-rame.htm, and The Merck Manual, Eighteenth Ed. 2006, the entire contents of which are hereby incorporated by reference.

[0141] In another embodiment, the compounds disclosed herein can be combined, with cytotoxic anti-cancer agents. Some non-limitingexamples of such agents can be found in the 13th Edition of the Merck Index (2001). These agents include, by no way of limitation, asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

[0142] Other cytotoxic drugs suitable for use with the compounds disclosed herein include, but are not limited to, those compounds acknowledged to be used in the treatment of neoplastic diseases, such as those for example in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition, 1996, McGraw-Hill). These agents include, by no way of limitation, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2,2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate,

fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

[0143] Other cytotoxic anti-cancer agents suitable for use in combination with the compounds disclosed herein also include newly discovered cytotoxic principles such as oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, temozolomide (Quinn et al., *J. Clin. Oncology*, **2003**, 21(4), 646-651), tositumomab (Bexxar®), trabedectin (Vidal et al., Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3181), and the inhibitors of the kinesin spindle protein Eg5 (Wood, et al. *Curr. Opin. Pharmacol.*, **2001**, 1, 370-377).

[0144] In another embodiment, the compounds disclosed herein can be combined with other signal transduction inhibitors. Some non-limiting examples of such agents include antibody therapies such as trastuzumab (HERCEPTIN®), cetuximab (ERBITUX®), ipilimumab (YERVOY®) and pertuzumab. Examples of such therapies also include, by no way of limitation, small-molecule kinase inhibitors such as imatinib (GLEEVEC®), sunitinib (SUTENT®), sorafenib (NEXAVAR®), erlotinib (TARCEVA®), gefitinib (IRESSA®), dasatinib (SPRYCEL®), nilotinib (TASIGNA®), lapatinib (TYKERB®), crizotinib (XALKORI®), ruxolitinib (JAKAFI®), vemurafenib (ZELBORAF®), vandetanib (CAPRELSA®), pazopanib (VOTRIENT®), afatinib, alisertib, amuvatinib, axitinib, bosutinib, brivanib, canertinib, cabozantinib, cediranib, crenolanib, dabrafenib, dacomitinib, danusertib, dovitinib, foretinib, ganetespib, ibrutinib, iniparib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, niraparib, oprozomib, olaparib, pictilisib, ponatinib, quizartinib, regorafenib, rigosertib, rucaparib, saracatinib, saridegib, tandutinib, tasocitinib, telatinib, tivantinib, tivozanib, tofacitinib, trametinib, vatalanib, veliparib, vismodegib, volasertib, BMS-540215, BMS777607, JNJ38877605, TKI258, GDC-0941 (Folkes, et al., J. Med. Chem., 2008, 51: 5522), BZE235, and others.

[0145] In another embodiment, the compounds disclosed herein can be combined with inhibitors of histone deacetylase. Some non-limiting examples of such agents

includesuberoylanilide hydroxamic acid (SAHA), LAQ-824 (Ottmann, et al. Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3024), LBH-589 (Beck, et al. Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3025), MS-275 (Ryan, et al. Proceedings of the American Association of Cancer Research **2004**, 45, abstract 2452), FR-901228 (Piekarz, et al. Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3028) and MGCDOl 03 (US 6,897,220).

[0146] In another embodiment, the compounds disclosed herein can be combined with other anti-cancer agents such as proteasome inhibitors, and mTOR inhibitors. These include, by no way of limitation, bortezomib, and CCI-779 (Wu, et al., Proceedings of the American Association of Cancer Research **2004**, 45, abstract 3849). The compounds disclosed herein can be combined with other anti-cancer agents such as topoisomerase inhibitors, including but not limited to camptothecin.

[0147] Those additional agents may be administered separately from the compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with the compound of this invention in a single composition. If administered as part of a multiple dosage regimen, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another which would result in the desired activity of the agents.

[0148] The amount of both the compound and the additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Normally, the amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent. In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically.

USES OF THE COMPOUNDS AND COMPOSITIONS DISCLOSED HEREIN

[0149] The invention features pharmaceutical compositions that include a compound of formula (I), ora compound listed in Table 1,and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of the compound in the compositions disclosed herein is such that is effective to detectably inhibit or molulate a protein kinase, such as PI3K or mTOR activity. The compounds disclosed herein are useful in therapy as antineoplasia agents or to minimize deleterious effects of PI3K or mTOR signaling.

[0150] The compounds disclosed herein would be useful for, but not limited to, the prevention or treatment of proliferative diseases, condition, or disorder in a patient by administering to the patient a compound or a composition disclosed herein in an effective amount. Such diseases, conditions, or disorders include cancer, particularly metastatic cancer, atherosclerosis and lung fibrosis.

[0151] The compounds disclosed herein would be useful for the treatment of neoplasm including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

[0152] The compounds also would be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and

neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

[0153] The compounds disclosed herein are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy. The compounds disclosed herein are also useful in the reduction of blood flow in a tumor in a subject. The compounds disclosed herein are also useful in the reduction of metastasis of a tumor in a subject.

[0154] Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats. As used herein, the compounds disclosed herein include the pharmaceutically acceptable derivatives thereof.

[0155] Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt and the like.

[0156] The treatment method that includes administering a compound or composition disclosed herein can further include administering to the patient an additional therapeutic agent (combination therapy) selected from: a chemotherapeutic or anti-proliferative agent, or an anti-inflammatory agent, wherein the additional therapeutic agent is appropriate for the disease being treated and the additional therapeutic agent is administered together with a compound or composition disclosed herein as a single dosage form or separately from the compound or composition as part of a multiple dosage form. The additional therapeutic agent may be administered at the same time as a compound disclosed herein or at a different time. In the latter case, administration may be staggered by, for example, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 1 month, or 2 months.

[0157] The invention also features a method of inhibiting the growth of a cell that expresses PI3K or mTOR, that includes contacting the cell with a compound or composition disclosed herein, thereby causing inhibition of growth of the cell. Some non-limiting examples of

a cell whose growth can be inhibited include: a breast cancer cell, a colorectal cancer cell, a lung cancer cell, a papillary carcinoma cell, a prostate cancer cell, a lymphoma cell, a colon cancer cell, a pancreatic cancer cell, an ovarian cancer cell, a cervical cancer cell, a central nervous system cancer cell, an osteogenic sarcoma cell, a renal carcinoma cell, a hepatocellular carcinoma cell, a bladder cancer cell, a gastric carcinoma cell, a head and neck squamous carcinoma cell, a melanoma cell, or a leukemia cell.

[0158] The invention provides a method of inhibiting or modulating the activity of PI3K or mTOR in a biological sample comprising contacting the biological sample with a compound or composition disclosed herein. The term "biological sample" as used herein, means a sample outside a living organism and includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition or modulation of kinase activity, particularly PI3K or mTOR activity, in a biological sample is useful for a variety of purposes known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0159] In certain embodiments of the present invention an "effective amount" or "effective dose" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of the aforementioned disorders. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorder or disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. A compound or composition can also be administered with one or more other therapeutic agents, as discussed above.

[0160] The compounds of this invention or pharmaceutical compositions thereof may also be used for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable

devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a compound of this invention.

[0161] Suitable coatings and the general preparation of coated implantable devices are described in U.S. Patent Nos. 6,099,562; 5,886,026; and 5,304,121, the contents of each of which are incorporated by reference herein. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics into the composition. Implantable devices coated with a compound of this invention are another embodiment of the present invention. The compounds may also be coated on implantable medical devices, such as beads, or co- formulated with a polymer or other molecule, to provide a "drug depot" thus permitting the drug to be released over a longer time period than administration of an aqueous solution of the drug.

GENERAL SYNTHETIC PROCEDURES

[0162] In order to illustrate the invention, the following examples are included. However, it is to be understood that these examples do not limit the invention and are only meant to suggest a method of practicing the invention.

[0163] Generally, the compounds in this invention may be prepared by methods described herein, wherein the substituents are as defined for formula (I), above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention. Persons skilled in the art will recognize that the chemical reactions described herein may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions.

Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[0164] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Arco Chemical Company and Alfa Chemical Company, Shanghai Medpep.Co Ltd, Aladdin-Shanghai Jinchun Reagents, Ltd, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou Xilong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tainjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[0165] Anhydrous THF, dioxane, toluene, and ether were obtained by refluxing the solvent with sodium. Anhydrous CH_2Cl_2 and $CHCl_3$ were obtained by refluxing the solvent with CaH_2. EtOAc, PE, hexanes, DMA and DMF were treated with anhydrous Na_2SO_4 prior use.

[0166] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[0167] Column chromatography was conducted using a silica gel column. Silica gel (300-400 mesh) was purchased from Qingdao Ocean Chemical Factory. ^1H NMR spectra were recorded with a Bruker 400 MHz spectrometer or a Bruker 600 MHz spectrometer at ambient temperature. ^1H NMR spectra were obtained as $CDCl_3$, DMSO-d_6, CD_3OD or acetone-d_6 solutions (reported in ppm), using TMS (0 ppm) or chloroform (7.26 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[0168] Low-resolution mass spectral (MS) data were generally determined on an Agilent 6120 Quadrupole HPLC-MS (Zorbax SB-C18, 2.1 x 30 mm, 3.5 micron, 6 minutes run, 0.6 mL/min flow rate, 5% to 95% (0.1% formic acid in CH_3CN) in (0.1% formic acid in H_2O)) with UV detection at 210nm/254 nm and electrospray ionization mode (ESI).

[0169] Purities of compounds were assessed by Agilent 1260 Pre-HPLC or Calesep Pump 250 Pre-HPLC (Column NOVASEP 50/80 mm DAC) with UV detection at 210nm/254 nm.

[0170] The following abbreviations are used throughout the specification:

ATP adenosine triphosphate

AcOH, HOAc, CH_3COOH acetic acid

AIBN azodiisobutyronitrile

BBr_3 boron tribromide

Bu_4NF tetrabutylammonium fluoride

BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BOC, Boc butyloxycarbonyl

BSA bovine serum albumin

n-BuOH butyl alcohol

n-BuLi *n*-butyllithium

$CDCl_3$ chloroform deuterated

CCl_4 carbon tetrachloride

$CHCl_3$ chloroform

CH_2Cl_2, DCM methylene chloride

CH_3SO_2Cl, MsCl 4-toluene sulfonyl chloride

Cs_2CO_3 Cesiumcarbonate

CH_3CN, MeCN acetonitrile

CH_3SO_2Cl, MsCl methanesulfonyl chloride

Cs_2CO_3 cesium carbonate

CuI cuprous iodide

DCC N,N'-Dicyclohexylcarbodie

DAST Diethylaminosulfur trifluoride

DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene

DEAD dimethyl azodicarboxylate

DIAD diisopropyl azodicarboxylate

DIBAL diisobutylaluminum hydride

DIEA, DIPEA, *i*-Pr_2NEt diisopropylethylamine

DMAP 4-dimethylaminopyridine

DME dimethoxyethane

DMF dimethylformamide

DMSO dimethylsulfoxide

DPPA diphenylphosphoryl azide

EDCI 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

EtOAc, EA ethyl acetate

EtOH ethanol

Et_2O diethyl ether

Et_3N, TEA triethylamine

FBS fetal bovine serum

g gram

h hour

HATU *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate

HBr hydrobromic acid

HBTU *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate

H_2O_2 hydrogen peroxide

HOAc,AcOH acetic acid

HOBt 1-hydroxybenzotriazole hydrate

i-Pr_2NH diisopropylamine

K_2CO_3 potassium carbonate

KOAc, CH_3COOK Potassium Acetate

LiHMDS lithium bis(trimethylsilyl)amide

LDA Lithium diisopropylamide

MCPBA *meta*-chloroperbenzoic acid

MeI methyl iodide

MeOH, CH_3OH methanol

2-MeTHF 2-methyl tetrahydrofuran

$MgSO_4$ magnesium sulfate

MsCl methanesulfonyl chloride

mL, ml milliliter

N_2 nitrogen

$NaBH_4$ sodium borohydride

$NaBH_3CN$ sodium cyanoborohydride

$NaClO_2$ sodium chlorite

NaH sodium hydride

Na_2CO_3 sodium carbonate

$NaHCO_3$ sodium bicarbonate

NaH_2PO_4 sodium biphosphate

NaO(*t*-Bu) sodium *tert*-butoxide

Na_2SO_4 sodium sulfate

NBS *N*-Bromosuccinimide

NIS *N*-Iodosuccinimide

NH_3 ammonia

NH_4Cl ammonium chloride

NMP *N*-methylpyrrolidinone

PBS phosphate buffered saline

P(*t*-Bu)$_3$ tri(tert-butyl)phosphine

Pd/C palladium on carbon

$Pd_2(dba)_3$ bis(dibenzylideneacetone) palladium

$Pd(dppf)Cl_2$ 1,1-bis(diphenylphosphino)ferrocene palladium dichloride

$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ dichloro[1,1'bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct

$Pd(PPh_3)_4$ palladium tetrakis triphenylphosphine

$Pd(PPh_3)_2Cl_2$ Bis(triphenylphosphine)palladium(II) chloride

PE petroleum ether (60-90 °C)

$POCl_3$ phosphorous oxychloride

PCl_5 phosphorus(V)chloride

PyBop benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

Pre-HPLC preparative high performance liquid chromatography

RT, rt, r.t. room temperature

Rt retention time

TBAB tetrabutylammonium bromide

TBAF tetrabutyl ammonium fluoride

$TBAHSO_4$ tetrabutylammonium hydrogen sulfate

TBTU *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate

TFA trifluoroacetic acid

TEAC bis(*tetra*-ethylammonium)carbonate

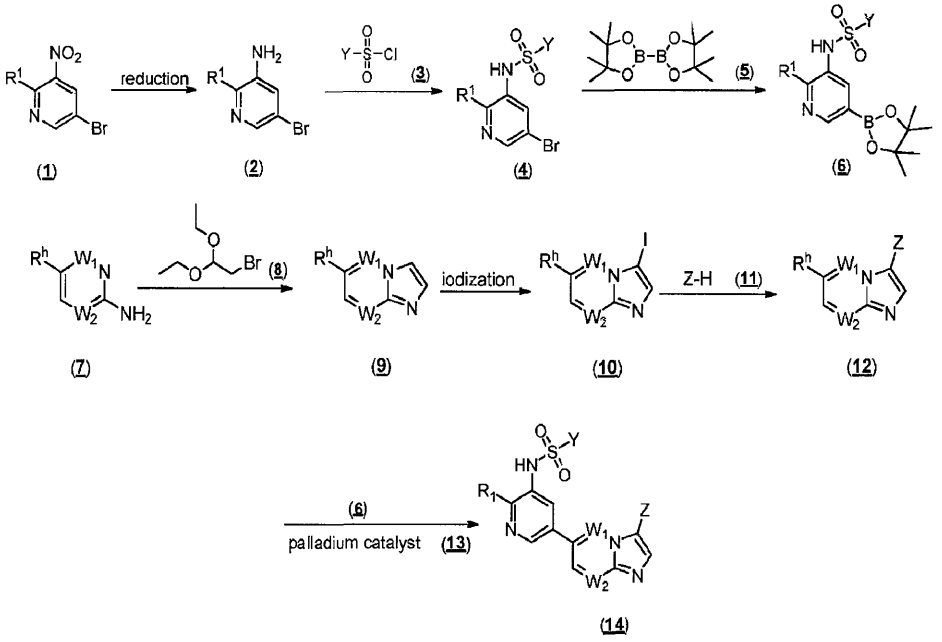
THF tetrahydrofuran

μL microliter

X-Phos 5-Bromo-4-chloro-3-indolylphosphat p-Toluidine salt

[0171] Representative synthetic procedures for the preparation of compounds of the disclosure are outlined below in following schemes. Unless otherwise indicated, R^1, W_1, W_2, Y and Z carry the definitions set forth above in connection with formula (I). R^h is Cl, Br, or I.

Scheme 1

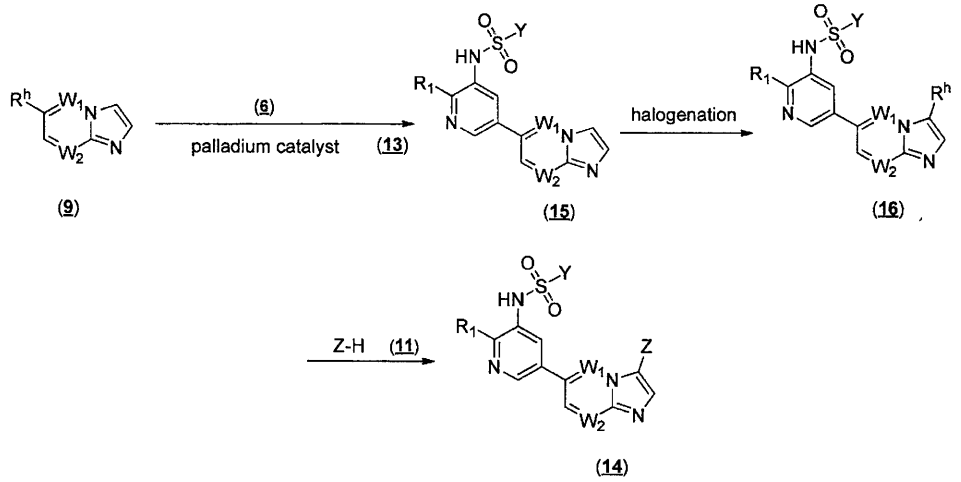


[0172] Some compounds with structures as defined in Formula (I) can be prepared by a general method as illustrated in Scheme 1. The nitropyridine derivative (**1**) is converted to aminopyridine (**2**) under reducing condition such as hydrogenation in the presence of catalyst

Pd/C or Fe powder in aqueous acidic conditions. Aminopyridine (2) is then coupled with sulfonyl chloride (3) to give sulfonamide (4) in the presence of a base such as Na_2CO_3, Et_3N, or pyridine in an aprotic solvent (for example, CH_2Cl_2, $CHCl_3$, etc.), or in pyridine with a catalytic amount of DMAP, or under the Schotten–Baumann condition. The subsequent coupling of sulfonamide (4) with bis(pinacolato)diboron (5) in the presence of an approporiate Pd catalyst leads to boronic ester (6).

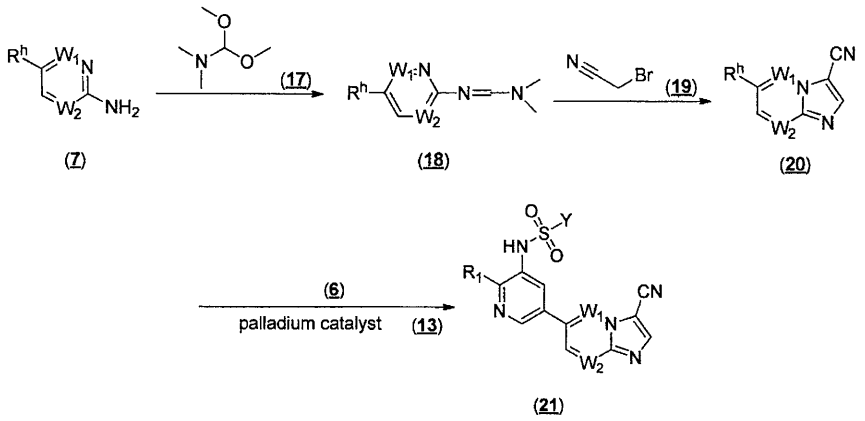
[0173] The synthesis of heteroaromatic core (12) having a bromo group is shown in Scheme 1. Bromo heteroaryl compound (7) is first condensed with acetal (8) to furnish bicyclic heteroaromatic compound (9) in an alcoholic solvent such as MeOH or EtOH. The subsequent iodination of (9) with N-iodosuccinimide at room temperature affords iodo compound (10). Compound (10) is then coupled with acetylene, cyanide or azide Z (11) to give heteroaromatic compound (12) under either basic conditions or in the presence of a Pd catalyst. The desired kinase inhibitors having formula (14) are obtained by the coupling of bromo heteroaromatic compound (12) with boronic ester (6) in the presence of an appropriate Pd catalyst.

Scheme 2



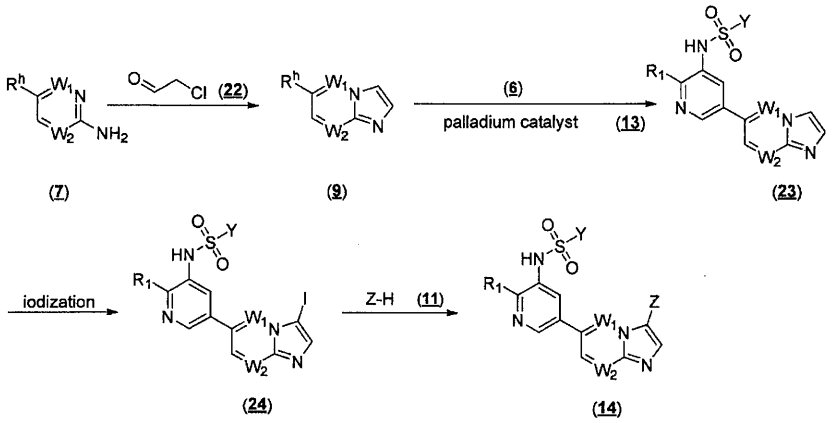
[0174] Alternatively, the compounds disclosed herein may be prepared by the method as described in Scheme 2. Bromo compound (9) is first coupled with boronic ester (6) to give biaryl compound (15) using an appropriate Pd complex as catalyst. Biaryl compound (15) is then treated with a halogenating agent (such as NIS) to afford compound (16). Coupling of compound (16) with compound (11) (i.e., acetylene deterivatives, cyanide or azide) under either basic conditions or in the presence of a Pd catalyst affords the desired kinase inhibitors (14).

Scheme 3



[0175] Scheme 3 shows another method to prepare the kinase inhibitors disclosed herein. Thus, substituted heteroaryl compound (7) having a bromo group can react with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (17) at an elevated temperature to provide enamine intermediate (18), which is further cyclized with alkyl halides (19) leading to nitrile (20). Coupling of nitrile (20) with boronic ester (6) in the presence of an appropriate Pd catalyst furnishes the desired kinase inhibitors (21).

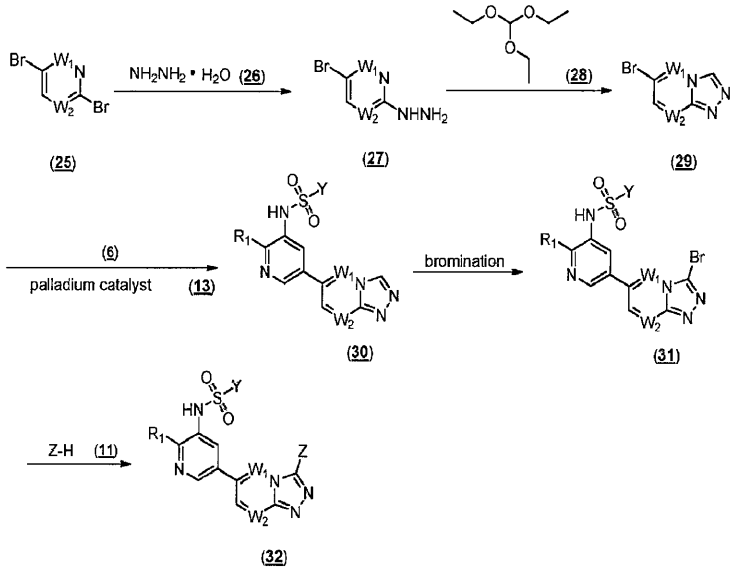
Scheme 4



[0176] The compounds disclosed herein can also be prepared using the synthetic route as shown in Scheme 4. Thus, bromo substituted heteroaryl compound (7) is first cyclized with 2-chloroacetaldehyde (22) at an elevated temperature to give compound (9). The coupling of compound (9) with boronic ester (6) in the presence of an appropriate Pd catalyst furnishes compound (23). The iodination of compound (23) with N-iodosuccinimide affords compound (24). Coupling of compound (24) with compound (11) (i.e., acetylene deterivatives, cyanide or azide) under either

basic conditions or in the presence of a Pd catalyst affords the desired kinase inhibitors (**14**).

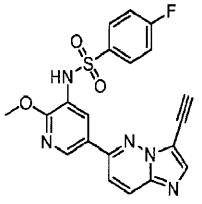
Scheme 5



[0177] Some compounds with structures as defined in Formula (I) can also be prepared by a general method as illustrated in Scheme 5 above. Compound (**25**) is first treated with hydrazine hydrate (**26**) at an elevated temperature to provide compound (**27**), which is subsequently cyclized with diethoxymethoxyethane (**28**) leading tobicyclic heteroaromatic (**29**). The coupling of compound (**29**) with the boronic ester (**6**) in the presence of an appropriate Pd catalyst gives compound (**30**). The bromination of compound (**30**) with N-bromosuccinimide affords compound (**31**). Coupling of compound (**31**) with compound (**11**) (i.e., acetylene deterivatives, cyanide or azide) under either basic conditions or in the presence of a Pd catalyst affords the desired kinase inhibitors (**32**).

EXAMPLES

Example 1 N-(5-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-4-fluorobenzenesulfonamide



Step 1) 6-bromoimidazo[1,2-b]pyridazine

[0178] To a solution of 6-bromopyridazin-3-amine (3.48 g, 20 mmol) in EtOH/H_2O (5/1, 180 mL) was added 2-bromo-1,1-diethoxyethane(11.8 g, 60 mmol), followed by p-toluenesulphonic acid (20.6 mg, 0.12 mmol). The mixture was stirred at 80 °C for 16 hours and then concentrated *in vacuo*. The resulted solid was washed with H_2O (4 mL), collected by filtration, and dried in a vacuum oven overnight at 40 °C to give the title compound as a gray solid (3.9 g, 100%).

MS (ESI, pos. ion) m/z: 198.1 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 9.6 Hz, 1H), 8.44 (d, J = 1.6 Hz, 1H), 8.33 (d, J = 1.9 Hz, 1H), 7.97 (d, J = 9.6Hz, 1H).

Step 2) 6-bromo-3-iodoimidazo[1,2-b]pyridazine

[0179] To a solution of 6-bromoimidazo[1,2-b]pyridazine (1.98 g, 10.0 mmol) in methanol (50 mL) at -10 °C was added N-iodosuccinimide (2.47 g, 11.0 mmol) in portions. The mixture was stirred at -10 °C for 30 minutes and then allowed to warm up to rt. The reaction was continued to stir at rt for 18 hours, and then concentrated *in vacuo*. The residue was dissolved in 100 mL of DCM and washed with 50 mL of aqueous Na_2CO_3 solution. The organic phase was concentrated *in vacuo* to give the title compound as a light yellow solid (2.0 g, 61%).

MS (ESI, pos. ion) m/z: 323.9 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.78 (d, J = 9.4 Hz, 1H), 7.21 (d, J = 9.4 Hz, 1H).

Step 3) 6-bromo-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine

[0180] To a susupension of 6-bromo-3-iodoimidazo[1,2-b]pyridazine (1.30 g, 4.0 mmol), ethynyltrimethylsilane (0.39 g, 4.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.28 g, 0.4 mmol) and CuI (0.076 g, 0.4 mmol) in 1,4-dioxane (60 mL) was added DIPEA (2.6 g, 20.0 mmol). The resulted mixture was stirred at 90 °C under N_2 atmosphere for 6 hours and then concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (385 mg, 33%).

MS (ESI, pos. ion) m/z: 294.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.80 (d, J = 9.4 Hz, 1H), 7.21 (d, J = 9.4 Hz, 1H), 0.32 (s, 9H).

Step 4) 4-fluoro-N-(2-methoxy-5-(3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-yl)pyridine-3-yl)benzenesulfonamide

[0181] To a suspension of 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (472.9 mg, 1.17 mmol), 6-bromo-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (309.0 mg, 1.1 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (85.7 mg, 0.11 mmol) in 1,4-dioxane (30 mL) was added a solution of Na_2CO_3 (556.5 mg, 5.25 mmol) in water (6 mL). The mixture was stirred at 90 °C under N_2 atmosphere for 1 hour, then cooled to rt and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as white powder (260 mg, 50%).

MS (ESI, pos. ion) m/z: 496.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 9.5 Hz, 1H), 8.00 (s, 1H), 7.91 (dd, J = 8.9 Hz, 5.0 Hz, 2H), 7.48 (d, J = 9.5 Hz, 1H), 7.14 (t, J = 8.5 Hz, 2H), 7.00 (s, 1H), 3.93 (s, 3H), 0.33 (s, 9H).

Step 5) N-(5-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-4-fluorobenzenesulfonamide

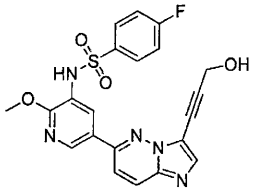
[0182] To a solution of 4-fluoro-N-(2-methoxy-5-(3-((trimethylsilyl)ethynyl)imidazo [1,2-b]pyridazin-6-yl)pyridine-3-yl)benzenesulfonamide (180.0 mg, 0.36 mmol) in THF (15 mL) was added 0.73 mL of TBAF (0.73 mmol, 1.0 M in THF). The resulted mixture was stirred at rt for 30 minutes and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 1/3) to give the title compound as a light yellow solid (74.5 mg, 48%).

MS (ESI, pos. ion) m/z: 424.1 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, J = 2.2Hz, 1H), 8.31 (d, J = 2.2Hz, 1H), 8.28 (d, J = 9.6 Hz, 1H), 8.14 (s, 1H), 7.95 (d, J = 9.6 Hz, 1H), 7.91 (dd, J = 8.9Hz, 5.2 Hz, 2H), 7.41 (t, J = 8.8Hz, 2H), 5.11 (s, 1H), 3.77 (s, 3H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 142.0, 138.9, 138.5, 136.4, 130.0, 129.9, 129.1, 126.4, 124.4, 121.2, 117.1, 116.5, 116.3, 111.8, 90.1, 70.1, 53.9.

Example 2 4-fluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step1) 3-(6-bromoimidazo[1,2-b]pyridazin-3-yl)prop-2-yn-1-ol

[0183] To a suspension of 6-bromo-3-iodoimidazo[1,2-b]pyridazine (1.48 g, 4.6 mmol), $Pd(PPh_3)_2Cl_2$ (322 mg, 0.46 mmol), CuI (87 mg, 0.46 mmol) and triethylamine (2.33 g, 23 mmol) in DMF (65 mL) was added prop-2-yn-1-ol (235 mg, 4.2 mmol). The mixture was stirred at rt under N_2 atmosphere for 4 hours and concentrated *in vacuo*. The residue was diluted with brine (150 mL) and extracted with EtOAc (60 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (580 mg, 50%).

MS (ESI, pos. ion) m/z: 252.1 $[M+H]^+$.

Step 2) 4-fluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-*b*]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

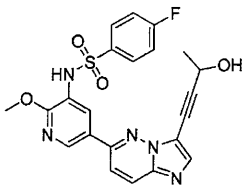
[0184] To a suspension of 3-(6-bromoimidazo[1,2-b]pyridazin-3-yl)prop-2-yn-1-ol (500 mg,2mmol), 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (900 mg, 2.2 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (164 mg, 0.2 mmol) in DME (40 mL) was added a solution of Na_2CO_3 (530 mg, 5 mmol) in H_2O (4 mL). The mixture was stirred at 70 °C under N_2 atmosphere for 4 hours, then cooled to rt, quenched with water (50 mL), and extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine (80 mL x 3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 30/1) to give the title compound as a yellow solid (110 mg, 12%).

MS (ESI, pos. ion) m/z: 454.0 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H), 4.49 (d, J = 5.9 Hz, 2H), 5.55 (t, J = 5.9 Hz, 1H),

7.42 (t, J = 8.8 Hz, 2H), 7.87-7.92 (m, 3H), 8.09 (s,1H), 8.27 (d, J = 9.6 Hz, 1H), 8.33 (d, J = 2.2 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 10.19 (s, 1H).

Example 3 4-fluoro-N-(5-(3-(3-hydroxybut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step1) 4-(6-bromoimidazo[1,2-b]pyridazin-3-yl)but-3-yn-2-ol

[0185] To a suspension of 6-bromo-3-iodoimidazo[1,2-b]pyridazine (520 mg, 1.6 mmol), $Pd(PPh_3)_2Cl_2$ (112 mg, 0.16 mmol), CuI (30 mg, 0.16 mmol) and DIPEA (1.04 g, 4.0 mmol) in DMF (24 mL) was added but-3-yn-2-ol (112 mg, 1.6 mmol). The resulted mixture was stirred at rt under N_2 atmosphere for 2 hours and then concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/DCM (v/v) = 1/50) to give the title compound as a yellow solid (210 mg, 50%).

MS (ESI, pos. ion) m/z: 266.0 $[M+H]^+$.

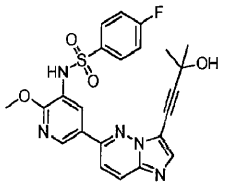
Step 2) 4-fluoro-N-(5-(3-(3-hydroxybut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0186] To a suspension of 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (354 mg, 0.87 mmol), 4-(6-bromoimidazo[1,2-b]pyridazin-3-yl)but-3-yn-2-ol (210 mg, 0.79 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (58 mg, 0.08 mmol) in DMF (21 mL) was added a solution of Na_2CO_3 (210 mg, 1.97 mmol) in water (4 mL). The mixture was stirred at 70 °C under N_2 atmosphere for 4 hours, then cooled to rt, quenched with H_2O (100 mL), and extracted with EtOAc (100 mL x 3). The combined organic phases were concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as a light brown solid (149 mg, 40%).

MS (ESI, pos. ion) m/z: 468.0 $[M+H]^+$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.17 (s, 1H), 8.70-8.69 (d, J = 2.2 Hz, 1H), 8.40-8.39 (d, J = 2.2 Hz, 1H), 8.28-8.26 (d, J = 9.5 Hz, 1H), 8.07 (s, 1H), 7.93-7.86 (m, 3H), 7.43-7.39 (t, J = 8.5 Hz, 2H), 5.67-5.66 (d, J = 5.4 Hz, 1H), 4.79-4.76 (m, 1H), 3.74 (s, 3H), 1.51-1.50 (d, J = 6.6 Hz, 3H).

Example 4 4-fluoro-N-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 4-(6-bromoimidazo[1,2-b]pyridazin-3-yl)-2-methylbut-3-yn-2-ol

[0187] To a suspension of 6-bromo-3-iodoimidazo[1,2-b]pyridazine (1.0 g, 3.0 mmol), $Pd(PPh_3)_2Cl_2$(0.2 g, 0.3 mmol), CuI (0.1 g, 0.6 mmol) and triethylamine (1 mL, 6 mmol) in DMF (15 mL) was added 2-methylbut-3-yn-2-ol (0.25 g, 3 mmol). The mixture was stirred at rt under N_2 atmosphere for 5 hours, then quenched with H_2O (40 mL), and extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a yellow solid (0.5 g, 58 %).

MS (ESI, pos. ion) m/z: 280.0 $[M+H]^+$.

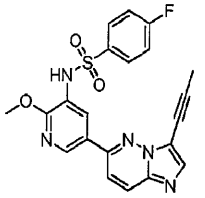
Step 2) 4-fluoro-N-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0188] To a suspension of 4-(6-bromoimidazo[1,2-b]pyridazin-3-yl)-2-methylbut-3-yn-2-ol (0.36 g, 1.3 mmol), 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.52 g, 1.3 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.1 g, 0.13 mmol) in DME (20 mL) was added a solution of Na_2CO_3 (0.28 g, 2.6 mmol) in H_2O (1.4 mL). The mixture was stirred at 100 °C under N_2 atmosphere overnight and then concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a yellow solid (0.4 g, 64 %).

MS (ESI, pos. ion) m/z: 482.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.73 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H), 8.28 (d, J = 9.5 Hz, 1H), 8.07 (s, 1H), 7.95 (d, J = 9.5 Hz, 1H), 7.87-7.84 (m, 2H), 7.43-7.39 (m, 2H), 3.73 (s, 3H), 1.58 (s, 6H).

Example 5 4-fluoro-N-(2-methoxy-5-(3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl)benzenesulfonamide



Step 1) 6-bromo-3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazine

[0189] To a suspension of 6-bromo-3-iodoimidazo[1,2-b]pyridazine (747 mg, 2.31 mmol), $Pd(PPh_3)_2Cl_2$ (161.5 mg, 0.23 mmol), CuI (44 mg, 0.23 mmol) and DIPEA (1.49 g, 11.55 mmol) in DMF (35 mL) was added Propyne (ca. 3% in Heptane) (20 mL, 4.44 mmol). The mixture was stirred at rt under N_2 atmosphere for 2 hours, then quenched with H_2O (100 mL), and extracted with EtOAc (100 mL x 3). The combined organic phases were concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (pure DCM) to give the title compound as a yellow solid (400 mg, 73.6%).

MS (ESI, pos. ion) m/z: 236.0 $[M+H]^+$.

Step 2) 4-fluoro-N-(2-methoxy-5-(3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl) benzenesulfonamide

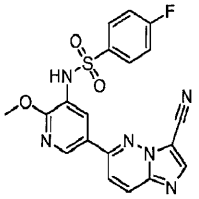
[0190] To a suspension of 6-bromo-3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazine (400 mg, 1.70 mmol) in DMF (30 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (125 mg, 0.17 mmol). The mixture was stirred at rt under N_2 atmosphere for 0.5 hours. A solution of 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (760 mg, 1.86 mmol) in DMF (15 mL) was added to the reaction mixture, followed by adding a solution of Na_2CO_3 (450 mg, 4.25 mmol) in H_2O (11 mL). The resulted mixture was stirred at 70 °C under N_2 atmosphere for 4 hours, then cooled to rt, quenched with H_2O (100 mL), and extracted with EtOAc (100 mL x 3). The combined organic phases were concentrated *in vacuo*.

The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 200/1) to give the crude product as a brown solid. The solid was washed with H_2O (10 mL), followed by EtOH (5 mL) to give the title compound as a light brown solid (262 mg, 35.3%).

MS (ESI, pos. ion) m/z: 438.1 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 10.18 (s, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.35 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 9.5 Hz, 1H), 8.01 (s, 1H), 7.89-7.86 (m, 3H), 7.41 (t, J = 8.5 Hz, 2H), 3.75 (s, 3H), 2.26 (s, 3H).

Example 6 N-(5-(3-cyanoimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-4-fluorobenzenesulfonamide



Step 1) N'-(6-bromopyridazin-3-yl)-N,N-dimethylformimidamide

[0191] A mixture of 6-bromopyridazin-3-amine (1.74 g, 10 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (1.3 g, 11 mmol) was stirred at 100 °C for 3 hours. The mixture was cooled to room temperature and solidified upon standing. The solid was filtered and dried *in vacuo* to give the title compound as a gray solid (1.85g, 100%).

Step 2) 6-bromoimidazo[1,2-b]pyridazine-3-carbonitrile

[0192] To a solution of N'-(6-bromopyridazin-3-yl)-N,N-dimethylformimidamide (1.23 g, 5.41 mmol) in acetonitrile (15 mL) was added bromoacetonitrile (1.13 mL, 16.25 mmol). The mixture was stirred at 80 °C overnight and then concentrated *in vacuo*. The residue was dissolved in a mixture of acetonitrile (15 mL) and DIPEA (6.0 mL, 35.60 mmol). The resulted mixture was stirred at rt for 4 hours and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (0.9 g, 75%).

MS (ESI, pos. ion) m/z: 222.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ8.22 (s, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 9.5 Hz, 1H).

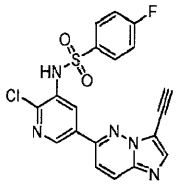
Step 3) N-(5-(3-cyanoimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-4-fluorobenzenesulfonamide

[0193] To a mixture of 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (612 mg, 1.5 mmol), 6-bromoimidazo[1,2-b] pyridazine-3-carbonitrile (222 mg, 1.0 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (81.6 mg, 0.1 mmol) and Na_2CO_3 (424 mg, 4.0 mmol) were added 1,4-dioxane (25 mL) and water (5 mL). The mixture was stirred at 90 °C under N_2 atmosphere for 5 hours, then cooled to rt and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a light yellow solid (400 mg, 94%).

MS (ESI, pos. ion) m/z: 425.0 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3H), 7.41-7.48 (m, 2H), 7.89-7.97 (m, 2 H), 8.16 (d, J = 9.7 Hz, 1H), 8.30 (d, J = 2.2 Hz, 1H), 8.46 (d, J = 9. 6 Hz, 1H), 8.61 (s, 1H), 8.72(d, J = 2.2 Hz, 1H).

Example 7 N-(2-chloro-5-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide



Step 1) N-(2-chloro-5-(3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide

[0194] To a mixture of (6-chloro-5-(4-fluorophenylsulfonamido)pyridin-3-yl)boronic acid (521.0 mg, 1.58 mmol), 6-bromo-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (370.0 mg, 1.26 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (71 mg, 0.087 mmol) and Na_2CO_3 (433 mg, 4.1 mmol) in 1,4-dioxane (20 mL) was added water (4 mL). The mixture was stirred at 90 °C under N_2 atmosphere for 1 hour, then cooled to rt, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as white powder (110 mg, 11.5%).

MS (ESI, pos. ion) m/z: 500.0 $[M+H]^+$.

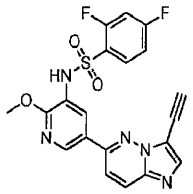
Step 2) N-(2-chloro-5-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide

[0195] To a solution of N-(2-chloro-5-(3-((trimethylsilyl)ethynyl)imidazo[1,2-b] pyridazin-6-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide (250.0 mg, 0.5 mmol) in THF (20 mL) was added 1mL of TBAF (1 mmol, 1.0 M in THF). The resulted mixture was stirred at rt for 1 hour, then concentrated *in vacuo*. The residue was purified by a preparative HPLC to give the title compound as a light yellow solid (80 mg, 37.6%).

MS (ESI, pos. ion) m/z: 428.0 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 5.11 (s, 1H), 7.42-7.48 (t, J = 8.7 Hz, 2H), 7.87-7.91 (m, 2H), 8.00-8.03 (d, J =9.6 Hz, 1H), 8.19 (s, 1H), 8.35-8.42 (m, 2H), 8.95 (s, 1H), 10.65 (s, 1H).

Example 8 N-(5-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide



Step 1) 2,4-difluoro-N-(2-methoxy-5-(3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl)benzenesulfonamide

[0196] To a mixture of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (349.0 mg, 0.82 mmol), 6-bromo-3-((trimethylsilyl)ethynyl)imidazo[1,2-b]pyridazine (200.0 mg, 0.64 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (55.6 mg, 0.064 mmol) and Na_2CO_3 (338.8 mg, 3.196 mmol) in 1,4-dioxane (18 mL) was added water (3 mL). The mixture was stirred at 90 °C under N_2 atmosphere for 1 hour, then cooled to rt, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (160 mg, 46%).

MS (ESI, pos. ion) m/z: 514.0 $[M+H]^+$.

Step 2) N-(5-(3-ethynylimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-2,4-

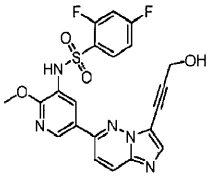
difluorobenzenesulfonamide

[0197] To a solution of 2,4-difluoro-N-(2-methoxy-5-(3-((trimethylsilyl)ethynyl)imidazo [1,2-b]pyridazin-6-yl)pyridin-3-yl)benzenesulfonamide (230.0 mg, 0.45 mmol) in THF (20 mL) was added 0.9 mL of TBAF (0.9 mmol, 1.0 M in THF). The solution was stirred at rt for 30 minutes, then concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 1/3) to give the title compound as a white solid (100 mg, 51%).

MS (ESI, pos. ion) m/z: 442.1 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 3H), 5.05 (s, 1H), 7.20-7.24 (t, J = 8.7 Hz, 1H), 7.56-7.60 (t, J = 8. 6 Hz, 1H), 7.78-7.84 (q, J =8.3 Hz, 1H), 7.94-7.96 (d, J = 9.6 Hz, 1H), 8.13 (s, 1H), 8.28-8.30 (m, 2H), 8.73-8.74 (d, J = 2.0 Hz, 1H).

Example 9 2,4-difluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



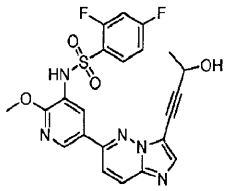
[0198] To a suspension of 3-(6-bromoimidazo[1,2-b]pyridazin-3-yl)prop-2-yn-1-ol (1.69 g, 6.72 mmol) and $Pd(PPh_3)_2Cl_2 \cdot CH_2Cl_2$ (549 mg, 0.672 mmol) in DME (70 mL) was added a solution of Na_2CO_3 (1.78 g, 16.8 mmol) in water (20 mL), followed by adding a solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzene sulfonamide (3.15 g, 7.39 mmol) in DME (100 mL). The resulted mixture was stirred at 75 °C under N_2 atmosphere for 4 hours, then cooled to rt, quenched with water (300 mL), and extracted with EtOAc (200 mL x 4). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a yellow solid (1.3 g, 42%).

MS (ESI, pos. ion) m/z: 472.0 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.74-8.73 (d, J = 2.2 Hz, 1H), 8.30-8.27 (m, 2H), 8.06 (s, 1H), 7.92-7.90 (d, J = 9.5 Hz, 1H), 7.83-7.77 (m, 1H), 7.60-7.54 (m, 1H), 7.24-7.19

(m, 1H), 5.53-5.51 (m, 1H), 4.50-4.48 (d, J = 5.6 Hz, 1H), 3.72 (s, 3H).

Example 10 2,4-difluoro-N-(5-(3-(3-hydroxybut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

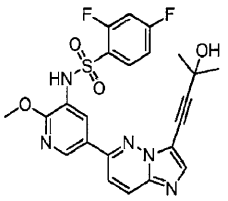


[0199] To a suspension of 4-(6-bromoimidazo[1,2-b]pyridazin-3-yl)but-3-yn-2-ol (400 mg, 1.50 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (123 mg, 0.15 mmol) and 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-yl)benzenesulfonamide (705 mg, 1.65 mmol) in DME (41 mL) was added a solution of Na_2CO_3 (398 mg, 3.76 mmol) in water (6 mL). The mixture was stirred at 75 °C under N_2 atmosphere for 3.5 hours, then cooled to rt, quenched with H_2O (200 mL), and extracted with EtOAc (200 mL x 4). The combined organic layers were concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a yellow solid (300 mg, 41%).

MS (ESI, pos. ion) m/z: 486.0 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.75-8.74 (d, J = 2.2 Hz, 1H), 8.36-8.35 (d, J = 2.2 Hz, 1H), 8.28-8.26 (d, J = 9.5 Hz, 1H), 8.06 (s, 1H), 7.93-7.91 (d, J = 9.5 Hz, 1H), 7.82-7.68 (m, 1H), 7.59-7.54 (m, 1H), 7.23-7.18 (m, 1H), 5.65-5.64 (d, J = 5.4 Hz, 1H), 4.80-4.74 (m, 1H), 3.72 (s, 3H), 1.50-1.49 (d, J = 6.6 Hz, 3H).

Example 11 2,4-difluoro-N-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 2,4-difluoro-N-(5-(imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0200] To a mixture of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (2.13 g, 5.0 mmol), 6-bromoimidazo[1,2-b]pyridazine (1 g, 0.79 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (408 mg, 0.5 mmol) and Na_2CO_3 (1.32 g, 12.5 mmol) were added DME (120 mL) and water (30 mL). The mixture was stirred at 70 °C under N_2 atmosphere for 4 hours, then cooled to rt; quenched with H_2O (500 mL), and then extracted with EtOAc (500 mL x 3). The combined organic phases were concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 200/3) to give the title compound as a light brown solid (1.28 g, 61.4%).

MS (ESI, pos. ion) m/z: 418.0 $[M+H]^+$.

Step 2) N-(5-(3-bromoimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0201] To a solution of 2,4-difluoro-N-(5-(imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (1.28 g, 3.07 mmol) in DMF (30 mL) was added NBS (545.8 mg, 3.07 mmol) in portions. The reaction was stirred at -20 °C for 12 hours and then quenched with H_2O (100 mL). The mixture was continued to stir overnight and then filtered. The solid was collected and purified by a preparative HPLC to give the title compound as a light yellow solid (320 mg, 21%).

MS (ESI, pos. ion) m/z: 496.1 $[M+H]^+$.

Step 3) 2,4-difluoro-N-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

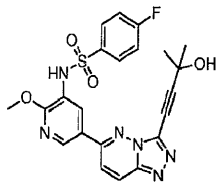
[0202] To a suspension of N-(5-(3-bromoimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (100 mg, 0.21 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and DIPEA (67 mg, 0.52 mmol) in DMF (2 mL) was added 2-methylbut-3-yn-2-ol (53 mg, 0.63 mmol). The mixture was stirred at rt under N_2 atmosphere for 6 hours and then concentrated *in vacuo*. The residue was purified by a preparative HPLC to give the title compound as a yellow solid (36 mg, 35%).

MS (ESI, pos. ion) m/z: 500.5 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 8.59-8.58 (d, J = 2.2 Hz, 1H), 8.46-8.45 (d, J = 2.2 Hz, 1H),

8.00-7.94 (m, 3H), 7.47 (s, 1H), 6.96-6.90 (m, 2H), 4.01 (s, 3H), 3.18(s, 1H), 2.97 (s, 1H), 1.57 (s, 6H).

Example 12 4-fluoro-N-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)-[1,2,4]triazolo[4,3-b] pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ol

[0203] A mixture of 3,6-dichloropyridazine (4.5 g, 30.4 mmol), hydrazinecarboxamide hydrochloride (6.7 g, 60.8 mmol) and three drop conc. HCl in EtOH (30 mL) was sealed in a microwave vial and heated in a microwave at 120 °C for 1 hour. The mixture was then cooled to rt and concentrated *in vacuo*. The residue was washed with H_2O (15 mL) and Et_2O (20 mL), then filterd, and the filter cake was dried *in vacuo* to give the title compound as a yellow solid (1.8 g, 32 %).

MS (ESI, pos. ion) m/z: 171.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 9.8 Hz, 1H), 7.20 (d, J = 9.8 Hz, 1H).

Step 2) 3,6-dichloro-[1,2,4]triazolo[4,3-b]pyridazine

[0204] A mixture of 6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ol (1.8 g, 10.6 mmol) and PCl_5 (0.4 g, 2 mmol) in $POCl_3$ (20 mL) was stirred at 120 °C for 12 hours and concentrated *in vacuo*. The residue was quenched with ice-water (50 mL) at 0 °C. The resulted mixture was extracted with EtOAc (50 mL x 2). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a pale yellow solid (0.5 g, 20 %).

MS (ESI, pos. ion) m/z: 189.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 9.7 Hz, 1H), 8.73 (d, J = 9.7 Hz, 1H).

Step 3) N-(5-(3-chloro-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-4-

fluorobenzenesulfonamide

[0205] To a suspension of 3,6-dichloro-[1,2,4]triazolo[4,3-b]pyridazine (0.5 g, 1.8 mmol), 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.8 g, 2.2 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.15 g, 0.18 mmol) in DME (20 mL) was added a solution of Cs_2CO_3 (1.2 g, 3.6 mmol) in H_2O (2 mL). The resulted mixture was stirred at 70 °C under N_2 atmosphere for 12 hours and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a pale yellow solid (0.5 g, 64%).

MS (ESI, pos. ion) m/z: 435.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.46 (d, J = 9.8 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 9.8 Hz, 1H), 7.90-7.87 (m, 2H), 7.42-7.38 (m, 2H), 3.79 (s, 3H).

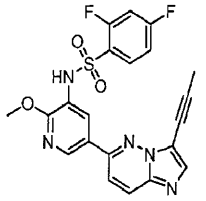
Step 4) 4-fluoro-N-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0206] A mixture of N-(5-(3-chloro-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-4-fluorobenzenesulfonamide (0.4 g, 0.96 mmol), 2-methylbut-3-yn-2-ol (0.16 g, 0.2 mmol), $Pd_2(dba)_3$ (0.04 g, 0.04 mmol), CuI (0.04 g, 0.16 mmol), *i*-Pr_2NH (0.29 g, 2.88 mmol) and X-Phos (0.09 g, 0.16 mmol) in DMF (20 mL) was stirred at 100 °C under N_2 atmosphere for 36 hours. The mixture was then concentrated *in vacuo* and the residue was purified by a slica gel column chromotagraphy (DCM/MeOH = 50/1) to give the title compound as a yellow solid (0.3 g, 68 %).

MS (ESI, pos. ion) m/z: 483.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 8.75 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 9.8 Hz, 1H), 8.44 (d, J = 2.2 Hz, 1H), 8.06 (d, J = 9.8 Hz, 1H), 7.87-7.84 (m, 2H), 7.43-7.38 (m, 2H), 3.75 (s, 3H), 1.60 (s, 6H).

Example 13 2,4-difluoro-N-(2-methoxy-5-(3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl)benzenesulfonamide



Step 1) 6-chloro-3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazine

[0207] To a suspension of 6-chloro-3-iodoimidazo[1,2-b]pyridazine (3 g, 10.7 mmol), $Pd(PPh_3)_2Cl_2$ (750 mg, 1.07 mmol), CuI (200 mg, 1.07 mmol), and diisopropylethylamine (7.5mL, 53.5 mmol) in 107 mL of DMF was added Propyne (ca. 3% in Heptane, 60 mL, 21.4 mmol). The mixture was stirred at rt under N_2 atmosphere for 4 hours, then H_2O (300 mL) was added and the resulted mixture was extracted with EtOAc (300 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (pure DCM) to provide the title compound as a yellow solid (560 mg, 27%).

MS (ESI, pos. ion) m/z: 192.3 $[M+H]^+$.

Step 2) 2,4-difluoro-N-(2-methoxy-5-(3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)pyridin-3-yl)benzenesulfonamide

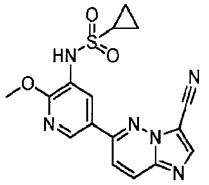
[0208] To a suspension of 6-chloro-3-(prop-1-yn-1-yl)imidazo[1,2-b]pyridazine (560 mg, 2.9 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (1.5 g, 3.5 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (237 mg, 0.29 mmol) in 1,4-dioxane/H_2O (30mL/6mL) was added Na_2CO_3 (774 mg, 7.3 mmol). The resulted mixture was purged with N_2 for three times and stirred at 90 °C sealed under N_2 atmosphere for 5 hours, then cooled to rt and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH(v/v) =100/1) to give the title compound as a light yellow solid (700 mg, 53%).

MS (ESI, pos. ion) m/z: 455.9 $[M+H]^+$; Purity: 97.6%;

^1H NMR (600 MHz, DMSO-d_6): δ 10.46 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.31 (d, J = 2.2 Hz, 1 H), 8.26 (d, J = 9.5 Hz, 1H), 8.01 (s, 1H), 7.89 (d, J = 9.5 Hz, 1H), 7.79 (d, J = 6.3 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.22 (td, J = 8.5, 2.2 Hz, 1H), 3.72 (s, 3H), 2.25 (s, 3H).

Example 14 N-(5-(3-cyanoimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)

cyclopropanesulfonamide



Step 1) 5-bromo-2-methoxy-3-nitropyridine

[0209] To a cooled solvent of MeOH (50.0 mL) was added Na (2.90 g, 126.4 mmol) portion-wise, then the mixture was warmed to rt and stirred until Na was all dissolved, then the solution was added to a suspension of 5-bromo-2-chloro-3-nitropyridine (10.0 g, 42.12 mmol, Shanghai long sheng hua gong, china) in MeOH (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then warmed up to rt and stirred further for 16 hours, then concentrated to 80 mL and quenched with water (100 mL). The precipitate was filtered, washed with water (50 mL x 2) and dried under infrared light to give the title compound as a pale yellow solid (9.62 g, 98 %).

MS (ESI, pos. ion) m/z: 233.0 $[M+H]^+$.

Step 2) 5-bromo-2-methoxypyridin-3-amine

[0210] To a suspension of 5-bromo-2-methoxy-3-nitropyridine (9.62 g, 41.3 mmol) in ethanol (100 mL) and water (10 mL) was added Iron powder (9.25 g, 165.2 mmol, Tianjin guangfukeji) and NH_4Cl (8.83 g, 165.2 mmol). The mixture was heated to reflux and stirred further for 15 hours, then cooled to rt, and concentrated *in vacuo.* The residue was dissolved in 250 mL of EtOAc and the resulted solution was washed with saturated aqueous sodium bicarbonate solution (100 mL), water (100 mL x 2) and brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the title compound as a yellow solid (8.16 g, 97 %).

MS (ESI, pos. ion) m/z: 202.8 $[M+H]^+$.

Step 3) N-(5-bromo-2-methoxypyridin-3-yl)cyclopropanesulfonamide

[0211] To a suspension of 5-bromo-2-methoxypyridin-3-amine (200 mg, 0.99 mmol) in pyridine (10 mL) was added cyclopropanesulfonyl chloride (346 mg, 2.46 mmol) slowly. The reaction was stirred at rt for 18 hours, then heated to 60 °C and stirred for 5 hours. The mixture

was cooled to rt, then acidified to pH = 2 with 1 M HCl (aq.), and the resulted mixture was extracted with DCM (15 mL x 3). The combined organic layers were washed with water (20 mL x 2) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc(v/v) = 5/1) to give the title compound as a yellow solid (191 mg, 63 %).

MS (ESI, pos. ion) m/z: 306.9 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, J = 2.22 Hz, 1H), 7.92 (d, J = 2.22 Hz, 1H), 6.70 (brs, 1H), 4.00 (s, 3H), 2.56-2.47 (m, 1H), 1.26-1.20 (m, 2H), 1.04-0.97 (m, 2H).

Step 4) N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl) cyclopropanesulfonamide

[0212] A solution of N-(5-bromo-2-methoxypyridin-3-yl)cyclopropanesulfonamide (50 mg, 0.163 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (166 mg, 0.652 mmol, Beijing datianfengtuo) and KOAc (64 mg, 0.652 mmol) in 1,4-dioxane (10 mL) was degassed and charged with N_2 for 3 times, then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (27 mg, 0.0326 mmol, matthey) was added. The mixture was heated to 80 °C and stirred further for 2.5 hours, then cooled to rt, concentrated *in vacuo* and the residue was dissolved in DCM (20 mL). The resulted mixture was filtered through a pad of CELITE®. The filtrate was washed with water (15 mL x 3) and brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/2) to give the title compound as a white solid (50 mg, 86 %).

MS (ESI, pos. ion) m/z: 355.1 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$): δ 8.30 (d, J = 1.65 Hz, 1H), 8.08 (d, J = 1.65 Hz, 1H), 6.64 (brs, 1H), 4.03 (s, 3H), 2.60-2.40 (m, 1H), 1.33 (s, 12H), 1.22-1.15 (m, 2H), 0.99-0.93 (m, 2H).

Step 5) N-(5-(3-cyanoimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl) cyclopropanesulfonamide

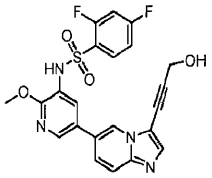
[0213] To a solution of 6-bromoimidazo[1,2-b]pyridazine-3-carbonitrile (50 mg, 0.23 mmol) in 1,4-dioxane (10 mL) were added N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)cyclopropanesulfonamide (88 mg, 0.25 mmol), Na_2CO_3 (48 mg,

0.46 mmol), H_2O (2 mL) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (37 mg, 0.046 mmol). The mixture was heated to 80 °C and stirred further for 1 hour, then cooled to rt, and concentrated *in vacuo*. The residue was extracted with DCM (10 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (DCM/MeOH (v/v) =200/1) to give the title compound as a light pink solid (60 mg, 72%).

MS (ESI, pos. ion) m/z: 371.0 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$): δ 8.60 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 8.27 (s, 1H), 8.16 (d, J = 9.6 Hz, 1H), 7.70 (d, J = 9.9 Hz, 1H), 6.85 (brs, 1H), 4.14 (s, 3H), 2.63-2.57 (m, 1H), 1.36-1.25 (s, 2H), 1.14-1.09 (m, 2H).

Example 15 2,4-difluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 6-bromoimidazo[1,2-a]pyridine

[0214] To a solution of 5-bromopyridin-2-amine (10.0 g, 57.7 mmol) in EtOH/H_2O (100 mL/20 mL) was added 2-chloroacetaldehyde (10.5g, 86.7 mmol) slowly. The mixture was heated to 80 °C and stirred further for 15 hours, then cooled to rt and concentrated *in vacuo*. The saturated aqueous $NaHCO_3$ solution (200 mL) was added to the residue. The resulted mixture was extracted with DCM (200 mL x 3). The combined organic phases were concentrated *in vacuo* to give the title compound as a brown solid (11.3 g, 100%).

MS (ESI, pos. ion) m/z: 197.1 $[M+H]^+$.

Step 2) 2,4-difluoro-N-(5-(imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl) benzenesulfonamide

[0215] A mixture of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (23.8 g, 55.2 mmol),

6-bromoimidazo[1,2-b]pyridazine (10.0 g, 50.8 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (4.15g, 5.1 mmol) and Na_2CO_3 (13.2 g, 127.5 mmol) in DME (250 mL) and water (50 mL) was degassed and charged with N_2 for 3 times. The mixture was heated to 70 °C and stirred for 6 hours, then cooled to rt, filtered through a pad of CELITE®, and the filtrate was concentrated *in vacuo*. The residue was purified by asilica column chromatography (pure EtOAc) to give the title compound as a white solid (15.1 g, 70.4%).

MS (ESI, pos. ion) m/z: 417.0 $[M+H]^+$.

Step 3) 2,4-difluoro-N-(5-(3-iodoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl) benzenesulfonamide

[0216] To a solution of 2,4-difluoro-N-(5-(imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (12.7 g, 30.5 mmol) in DMF (130 mL) was added NIS (17.2 g, 30.5 mmol) slowly. The mixture was stirred at 45 °C for 6 hours, then H_2O (150 mL) was added and stirred at rt further for 1 hour. Filtered and the filter cake was washed with EtOAc (20 mL) to give the title compound as a white solid (15.4 g, 90 %).

MS (ESI, pos. ion) m/z: 543.0$[M+H]^+$.

Step 4) 2,4-difluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

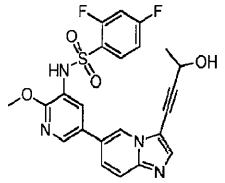
[0217] To a suspension of 2,4-difluoro-N-(5-(3-iodoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridine-3-yl)benzenesulfonamide (15.0 g, 27.6 mmol), $Pd(PPh_3)_2Cl_2$ (2.0 g, 2.9 mmol), CuI (0.55 g, 2.8 mmol) and Et_3N (14.0 g, 137.5 mmol) in 70 mL of DMF was added prop-2-yn-1-ol (5.6 g, 99.6 mmol). The mixture was stirred at 50 °C under N_2 atmosphere for 6 hours, then cooled to rt, filtered and the filtrate was concentrated *in vacuo*. H_2O (100 mL) was added to the residue and the resulted mixture was filtered. The filter cake was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the crude product, then the crude product was washed with EtOAc/MeOH (20 mL/10 mL) to give the title compound as a yellow solid (6.7 g, 50.4%).

MS (ESI, pos. ion) m/z: 471.0$[M+H]^+$;

^1H NMR (600 MHz, DMSO-d_6): δ 10.36 (s, 1H), 8.62 (s, 1H), 8.41 (d, J = 2.2 Hz, 1H), 7.98 (d,

J = 2.3 Hz, 1H), 7.83-7.71 (m, 1H), 7.87-7.50 (m, 3H), 7.68-7.50 (m, 1H), 7.22 (td, J = 8.5, 2.2 Hz, 1H), 5.48 (t, J = 5.9 Hz, 1H), 4.50 (d, J = 5.8 Hz, 2H), 3.66 (s, 3H).

Example 16 2,4-difluoro-N-(5-(3-(3-hydroxybut-1-yn-1-yl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

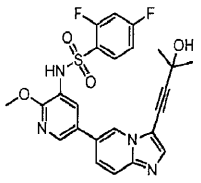


[0218] To a suspension of 2,4-difluoro-N-(5-(3-iodoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridine-3-yl)benzenesulfonamide (1.5 g, 2.7 mmol), $Pd(PPh_3)_2Cl_2$ (0.2 g, 0.3 mmol), CuI (0.06 g, 0.3 mmol) and Et_3N (1.4 g, 13.5 mmol) in 7 mL of DMF was added but-3-yn-2-ol (0.7 g, 9.9 mmol). The mixture was stirred at 50 °C under N_2 atmosphere for 6 hours, then cooled to rt, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a yellow solid (0.5 g, 40.1%).

MS (ESI, pos. ion) m/z: 485.1 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.10 (d, J = 1.9 Hz, 1H), 7.97 (t, J = 13.6 Hz, 1H), 7.90 (dd, J = 14.4, 8.3 Hz, 1H), 7.84 (s, 1H), 7.47 (d, J = 3.5 Hz, 1H), 7.37 (s, 1H), 6.97 (dt, J = 15.8, 8.2 Hz, 2H), 4.93 (q, J = 6.6 Hz, 1H), 4.03 (s, 3H), 3.49 (s, 1H), 1.65 (d, J = 6.6 Hz, 3H).

Example 17 2,4-difluoro-N-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



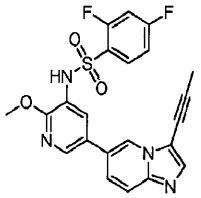
[0219] To a suspension of 2,4-difluoro-N-(5-(3-iodoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridine-3-yl)benzenesulfonamide (1.5 g, 2.7 mmol), $Pd(PPh_3)_2Cl_2$ (0.2 g, 0.3 mmol), CuI (0.06 g, 0.3 mmol) and Et_3N (1.4g, 13.5 mmol) in 7 mL of DMF was added 2-methylbut-3-yn-2-ol (0.8 g, 9.9 mmol). The mixture was stirred at 50 °C under N_2 atmosphere

for 6 hours, then cooled to rt, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a yellow solid (0.6 g, 40%).

MS (ESI, pos. ion) m/z: 499.1 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.38 (s, 1H), 8.52 (d, J = 0.7 Hz, 1H), 8.41 (d, J = 2.3 Hz, 1H), 7.97 (d, J = 2.3 Hz, 1H), 7.90 (s, 1H), 7.81-7.74 (m, 2H), 7.67 (dd, J = 9.3, 1.8 Hz, 1H), 7.61-7.56 (m, 1H), 7.22 (td, J = 8.5, 2.3 Hz, 1H), 5.71 (s, 1H), 3.68 (s, 3H), 1.57 (s, 6H).

Example 18 2,4-difluoro-N-(2-methoxy-5-(3-(prop-1-yn-1-yl)imidazo[1,2-a]pyridin-6-yl)pyridin-3-yl)benzenesulfonamide

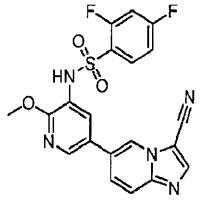


[0220] To a mixture of 2,4-difluoro-N-(5-(3-iodoimidazo[1,2-a]pyridin-6-yl)-2-methoxy pyridine-3-yl)benzenesulfonamide (1.50 g, 2.76 mmol), $Pd(PPh_3)_2Cl_2$ (0.189 g, 0.27 mmol) and CuI (52 mg, 0.27 mmol) in 20 mL of DMF was added diisopropylethylamine (1.78 g, 13.8 mmol). The mixture was degassed and charged with nitrogen for three times, then propyne (0.44 g, 11.04 mmol) was added by a syringe. The resulted mixture was stirred at 45 °C under N_2 atmosphere for 10 hours, and concentrated *in vacuo*. H_2O (40 mL) was added and the resulted mixture was stirred at rt for 1 hour, filtered and the filter cake was purified by a flash silica gel column chromatography (DCM/MeOH (v/v) = 300/1) to give the title compound as a yellow solid (220 mg, 17.52%).

MS (ESI, pos. ion) m/z: 454.9 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.46 (s, 1H), 9.18 (d, J = 7.3 Hz, 1H), 8.86 (s, 1H), 8.41 (s, 1H), 8.34 (s, 1H), 7.78 (dd, J = 14.6, 8.0 Hz, 1H), 7.72 (d, J = 7.3 Hz, 1H), 7.58 (t, J = 9.1 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 3.71 (s, 3H), 2.14 (s, 3H).

Example 19 N-(5-(3-cyanoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide



Step 1) N'-(5-chloropyridin-2-yl)-N,N-dimethylformimidamide

[0221] A mixture of 5-chloropyridin-2-amine (1.29 g, 10 mmol) and Dimethoxy-N,N -dimethylmethanamine (1.31 g, 11 mmol) was stirred at 100 °C for 3 hours, then cooled to rt, and a yellow solid was formed in the homogeneous solution. Filtered, and the filter cake was dried *in vacuo* to give the title compound as a yellow solid (1.85 g, 100%), the crude product was used in the next step without further purification.

MS (ESI, pos. ion) m/z: 184.0 $[M+H]^+$.

Step 2) 6-chloroimidazo[1,2-a]pyridine-3-carbonitrile

[0222] To a solution of N'-(5-chloropyridin-2-yl)-N,N-dimethylformimidamide (1.83 g, 10 mmol) in acetonitrile (30 mL) was added bromoacetonitrile (3.6 g, 30 mmol). The reaction was stirred at 80 °C overnight, then cooled to rt, and diisopropylethylamine (12.0 mL, 70 mmol) was added. The resulted mixture was stirred at rt for 4 hours and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (pure DCM) to give the title compound as a yellow solid (0.9 g, 51%).

MS (ESI, pos. ion) m/z: 178.0 $[M+H]^+$.

Step 3) N-(5-(3-cyanoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

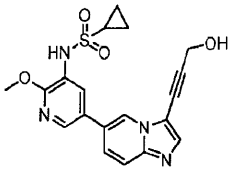
[0223] A mixture of 6-chloroimidazo[1,2-a]pyridine-3-carbonitrile (900 g, 5.07 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzene sulfonamide (3.24 g, 7.06 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (416 mg, 0.51 mmol) and Na_2CO_3 (2.15 g, 20.28 mmol) was degassed and charged with N_2 for 3 times, followed by adding 1,4-dioxane (125 mL) and water (25 mL). The mixture was degassed and charged with N_2 for 3 times, then heated to 90 °C and stirred further for 6 hours. After cooling to rt, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) =2/1) to give the title compound as a light brown solid (280

mg, 12%).

MS (ESI, pos. ion) m/z: 442.1 $[M+H]^+$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.24 (s, 1H), 8.11 (s, 1H), 7.95 (q, *J* = 8.7 Hz, 3H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.38 (s, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 6.99 (t, *J* = 9.2 Hz, 1H), 4.02 (s, 3H).

Example 20 N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide



Step 1) N-(5-(imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide

[0224] To a solution of 6-bromoimidazo[1,2-a]pyridine (318 mg, 1.61 mmol) in 1,4-dioxane (15 mL) were added N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)cyclopropanesulfonamide (600 mg, 1.69 mmol), KOAc (316 mg, 3.22 mmol), H_2O (3 mL) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (131 mg, 0.161 mmol). The reaction was heated to 85 °C and stirred further for 5 hours under N_2 atmosphere, then cooled to rt, and concentrated *in vacuo*. The residue was dissolved in DCM (200mL) and the resulted mixture was filtered through a CELITE®. The filtrate was washed with H_2O (100 mL) and brine (100 mL). The combined aqueous layers were extracted with DCM (50 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (DCM/MeOH (v/v) =65/1) to give the title compound as a yellowish solid (342 mg, 62%).

MS (ESI, pos. ion) m/z: 345.0 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.42 (s, 1H), 8.91 (s, 1H), 8.35 (d, *J* = 2.1 Hz, 1H), 7.99 (s, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 7.68-7.61 (m, 2H), 7.54 (dd, *J* = 1.8, 9.6 Hz, 1H), 3.98 (s, 3H), 2.82-2.74 (m, 1H), 1.00-0.89 (m, 4H).

Step 2) N-(5-(3-iodoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)

cyclopropanesulfonamide

[0225] To a solution of N-(5-(imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl) cyclopropanesulfonamide (292 mg, 0.85 mmol) in acetonitrile (20 mL) was added NIS (210 mg, 0.933 mmol) at 0 °C. The mixture was heated to 84 °C and stirred further for 1 hour, then cooled to rt, and filtered. The filter cake was dried *in vacuo* to give the crude product, and the filtrate was concentrated *in vacuo*. The residue was dissolved in DCM (20 mL). The resulted mixture was washed with $Na_2S_2O_3$ (aq., 10%, 10 mL), Na_2CO_3 (aq., 1M, 10 mL), H_2O (10 mL) and brine (10 mL), and extracted with DCM (10 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue together with the above crude product were purified by a flash silica gel column chromatography (DCM/MeOH (v/v) =95/1) to give the title compound as a white solid (293 mg, 73%).

MS (ESI, pos. ion) m/z: 471.0 $[M+H]^+$;

^1H NMR (600 MHz, DMSO-d_6): δ 9.44 (s, 1H), 8.39 (d, J = 2.4 Hz, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.77 (s, 1H), 7.73 (d, J = 9.3 Hz, 1H), 7.61 (dd, J = 1.8, 9.3 Hz, 1H), 3.99 (s, 3H), 2.88-2.72 (m, 1H), 0.98-0.92 (m, 4H).

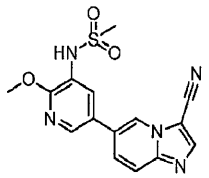
Step 3) N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide

[0226] To a suspension of N-(5-(3-iodoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide (85 mg, 0.18 mmol), CuI (20.6 mg, 0.108 mmol) and $Pd(PPh_3)_4$ (41.6 mg, 0.036 mmol) in DMF (3 mL) were added triethylamine (0.05 mL, 0.36 mmol) and prop-2-yn-1-ol (0.03 mL, 0.54 mmol). The mixture was degassed and charged with argon for 3 times, then stirred at rt for 2.5 hours, diluted with EtOAc (10 mL), and filtered through a CELITE®. The filtrate was washed with aqueous sodium bicarbonate solution (20 mL) and H_2O (20 mL). The combined aqueous layers were extracted with DCM (10 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (DCM/MeOH (v/v) =50/1) to give the title compound as a yellow solid (50 mg, 69%).

MS (ESI, pos. ion) m/z: 399.0 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.45 (s, 1H), 8.66 (brs, 1H), 8.40 (d, J = 2.19 Hz, 1H), 7.95 (d, J = 2.16 Hz, 1H), 7.80 (brs, 1H), 7.68 (brs, 1H), 5.46 (t, J = 6.06 Hz, 1H), 4.48 (d, J = 4.86 Hz, 2H), 3.99 (s, 3H), 2.83-2.74 (m, 1H), 0.97-0.91 (m, 4H).

Example 21 N-(5-(3-cyanoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl) methanesulfonamide



Step 1) N-(5-bromo-2-methoxypyridin-3-yl)methanesulfonamide

[0227] To a suspension of 5-bromo-2-methoxypyridin-3-amine (8.16 g, 40.2 mmol) in DCM (100 mL) was added pyridine (9.71 mL, 120.6 mmol), followed by adding a solution of methanesulfonyl chloride (7.78 mL, 100.5 mmol) in DCM (20 mL) drop-wise at rt. The reaction was stirred at rt for 24 hours and quenched with aqueous HCl solution (1 M, 30 mL). The resulted mixture was extracted with DCM (15 mL x 2). The combined organic phases were washed with water (50 mL x 2) and concentrated *in vacuo*. The residue was dissolved in methanol (50 mL), then aqueous NaOH solution (2M, 50 mL) was added and the mixture stirred at rt for 30 minutes. The methanol was removed under reduced pressure and the aqueous phase was extracted with DCM (30 mL x 4). The aqueous phase was then acidified to pH = 2 with aqueous HCl solution (2 M). The resulted precipitate was collected by filtration to give the title compound as a white solid (6.40 g, 57 %).

MS (ESI, pos. ion) m/z: 280.8 $[M+H]^+$.

Step 2) N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-yl) methanesulfonamide

[0228] A suspension of N-(5-bromo-2-methoxypyridin-3-yl)methanesulfonamide (3.35 g, 11.9 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.24 g, 16.7 mmol, Beijing datianfengtuo) in toluene (100 mL) was degassed and charged with N_2 for 3 times, then $Pd(dba)_3$ (616 mg, 0.595 mmol, Matthey) and PPh_3 (243 mg, 0.892 mmol) were added. The mixture was heated to 45 °C and stirred for 45 minutes, then KOAc (3.74 g, 23.8 mmol) was

added. The resulted mixture was heated to reflux and stirred further for 3 hours, then cooled to rt, diluted with EtOAc (100 mL), and filtered through a CELITE®. The filtrate was washed with water (70 mL x 3) and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (2.90 g, 74 %).

MS (ESI, pos. ion) m/z: 328.9 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$): δ 8.32 (d, J = 1.4 Hz, 1H), 8.06 (d, J = 1.3 Hz, 1H), 6.66 (brs, 1H), 4.05 (s, 3H), 3.02 (s, 3H), 1.33 (s, 12H).

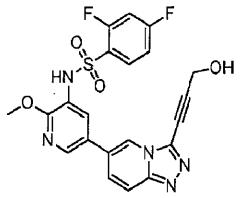
Step 3) N-(5-(3-cyanoimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)methanesulfonamide

[0229] A suspension of 6-bromoimidazo[1,2-a]pyridine-3-carbonitrile (50 mg, 0.22 mmol) in 1,4-dioxane/water (5 mL/1 mL) was degassed and charged with N_2 three times, then $Pd(dppf)Cl_2$ (37 mg, 0.045 mmol), N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanesulfonamide (111 mg, 0.338 mmol) and Na_2CO_3 (48 mg, 0.450 mmol) were added to the mixture successively. The mixture was heated to reflux and stirred further for 65 minutes, then cooled to rt, and concentrated *in vacuo*. The residue was dissolved in DCM (20 mL) and water (20 mL). The resulted mixture was separated, and the aqueous layer was extracted with DCM (10 mL x 2). The combined organic phases were washed with water (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as a light pink solid (35 mg, 46 %).

MS (ESI, pos. ion) m/z: 344.0 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.25 (brs, 1H), 8.17 (d, J = 2.28 Hz, 1H), 7.99 (d, J = 2.28 Hz, 1H), 7.86 (d, J = 8.91 Hz, 1H), 7.63 (dd, J = 1.59, 9.24 Hz, 1H), 6.86 (s, 1H), 4.10 (s, 3H), 3.07 (s, 3H).

Example 22 2,4-difluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 5-bromo-2-hydrazinylpyridine

[0230] To a solution of 2,5-dibromopyridine (10.50 g, 44 mmol) in 210 mL of pyridine was added hydrazine hydrate (80%, 8.85 g, 176.4 mmol), and the mixture was heated to 110 °C and stirred further for 2 hours, then cooled to rt, and concentrated *in vacuo*. The residue was diluted with DCM (1500 mL). The resulted mixture was washed with aqueous NaOH solution (1 M, 350 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the title compound as a gray solid (7.87 g, 94.8%).

MS (ESI, pos. ion) m/z: 188.0$[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (d, J = 2.3 Hz, 1H), 7.67 (s, 1H), 7.59 (dd, J = 8.9, 2.5 Hz, 1H), 6.69 (d, J = 8.9 Hz, 1H), 4.16 (s, 2H).

Step 2) 6-bromo-[1,2,4]triazolo[4,3-a]pyridine

[0231] To a mixture of 5-bromo-2-hydrazinylpyridine (7.87 g, 42 mmol) in 200 mL of diethoxymethoxyethane was added p-toluenesulfonicacid (0.30 g, 1.7 mmol), and the mixture was heatedto 110 °C and stirred further for 20 hours, then cooled to rt, and concentrated *in vacuo*. The residue was diluted with H_2O (150 mL). The resulted mixture was washed with aqueous $NaHCO_3$ solution (saturated, 40 mL), and extracted with DCM (300 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*.The residue was purified by a flash silica gel chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (6.60 g, 79.77%).

MS (ESI, pos. ion) m/z: 197.9 $[M+H]^+$;

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.34 (s, 1H), 7.75 (d, J = 9.7 Hz, 1H), 7.36 (d, J = 9.7 Hz, 1H).

Step 3) N-(5-([1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0232] To a mixture of 6-bromo-[1,2,4]triazolo[4,3-a]pyridine (3.00 g, 15.2 mmol) in 65 mL of 1,4-dioxane was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.24 g, 1.52 mmol) and a solution of sodium carbonate (4.00 g, 38 mmol) in 13 mL of water, and the mixture was degassed and charged with N_2 for 3 times, then stirred at rt for a while, followed by addition of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzene sulfonamide (7.78 g, 18.2 mmol), the mixture was degassed and charged with nitrogen for 3 times, then heated to 90 °C and stirred overnight. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as a gray solid (3.00 g, 47.33%).

MS (ESI, pos. ion) m/z: 418.1 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$): δ 10.36 (s, 1H), 9.26 (s, 1H), 8.91 (s, 1H), 8.39 (d, J = 2.3 Hz, 1H), 7.97 (d, J = 2.3 Hz, 1H), 7.88 (d, J = 9.5 Hz, 1H), 7.76 (td, J = 8.5, 6.5 Hz, 1H), 7.70 (dd, J = 9.6, 1.7 Hz, 1H), 7.61-7.54 (m, 1H), 7.24-7.15 (m, 1H), 3.64 (s, 3H).

Step 4) N-(5-(3-bromo-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0233] To a solution of N-(5-([1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (6.60 g, 15.83 mmol) in $CHCl_3$ (130 mL) was added N-bromosuccinimide (2.96 g, 16.62 mmol) at -5 °C slowly and stirred for 3 hours. The reaction mixturewere concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a white solid (2.80 g, 37.32%).

MS (ESI, pos. ion) m/z: 495.8 $[M+H]^+$.

Step 5) 2,4-difluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

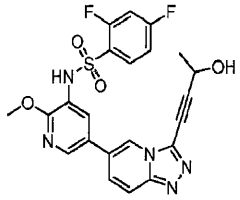
[0234] To a mixture of N-(5-(3-bromo-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (0.85 g, 1.79 mmol), $Pd(PPh_3)_2Cl_2$ (0.126 g, 0.18 mmol) and CuI (34 mg, 0.18 mmol) in 8 mL of DMF was added triethylamine (0.904 g, 8.95 mmol), and the mixture was degassed and charged with nitrogen for 3 times, then

prop-2-yn-1-ol (0.300 g, 5.37 mmol) was added by a syringe. The mixture was stirred at 50 °C under N_2 atmosphere overnight, then cooled to rt, and concentrated *in vacuo*. The residue was diluted with water (25 mL). The resulted mixture was filtered and the filter cake was further purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a yellow solid (0.28 g, 33.21%).

MS (ESI, pos. ion) m/z: 471.8$[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.38 (s, 1H), 8.77 (s, 1H), 8.04-7.48 (m, 4H), 7.24 (t, J = 7.6 Hz, 1H), 5.47 (d, J = 5.0 Hz, 1H), 4.58-4.39 (m, 1H), 3.67 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H).

Example 23 2,4-difluoro-N-(5-(3-(3-hydroxybut-1-yn-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



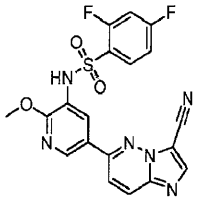
[0235] To a mixture of N-(5-(3-bromo-[1,2,4]triazolo[4,3-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide(0.85 g, 1.79 mmol), $Pd(PPh_3)_2Cl_2$ (0.126 g, 0.18 mmol) and CuI (34 mg, 0.18 mmol) in 8 mL of DMF was added triethylamine (0.904 g, 8.95 mmol), and the mixture was degassed and charged with nitrogen for 3 times, then but-3-yn-2-ol (0.376 g, 5.37 mmol) was added by a syringe. The mixture was stirred at 50 °C under N_2 atmosphere overnight, then cooled to rt, and concentrated *in vacuo*. The residue was diluted in water (25 mL). The resulted mixture was filtered and the filter cake was further purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a yellow solid (0.28 g, 32.25%).

MS (ESI, pos. ion) m/z: 485.9$[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.38 (s, 1H), 8.77 (s, 1H), 8.04-7.48 (m, 4H), 7.24 (t, J = 7.6 Hz, 1H), 5.47 (d, J = 5.0 Hz, 1H), 4.58-4.39 (m, 1H), 3.67 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H).

Example 24 N-(5-(3-cyanoimidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)-2,4-

difluorobenzenesulfonamide



[0236] 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (1.47 g, 3.45 mmol), 6-bromoimidazo[1,2-b]pyridazine-3-carbonitrile (513 mg, 2.3 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (188 mg, 0.23mmol) and Na_2CO_3 (975 mg, 9.2 mmol) were placed into a two-neck flask, and the mixture was degassed and charged with N_2 for 3 times, followed by adding 1,4-dioxane (50 mL) and water (10 mL). The resulted mixture was degassed and charged with N_2 for 3 times, then heated to 90 °C and stirred further for 5 hours. The mixture was then cooled to room temperature, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) =2/3) to give the title compound as a light yellow solid (580 mg, 57%).

MS (ESI, pos. ion) m/z: 443.2$[M+H]^+$; Purity: 97.1%;

^1H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.77 (d, J = 2.3 Hz, 1H), 8.60 (s, 1H), 8.46 (d, J = 9.6 Hz, 1H), 8.29 (d, J = 2.3 Hz, 1H), 8.17 (d, J = 9.7 Hz, 1H), 7.86-7.81 (m, 1H), 7.61-7.53 (m, 1H), 7.24 (td, J = 8.4, 2.0 Hz, 1H), 3.76 (s, 3H).

BIOLOGICAL TESTING

[0237] The efficacy of the compounds disclosed herein as inhibitors of PI3 kinases and mTOR kinases can be evaluated as follows. The assay results demonstrate that certain compounds disclosed herein potently inhibit PI3Ks and mTOR.

[0238] The LC/MS/MS system used in the analysis consists of an Agilent 1200 Series vacuum degasser, binary pump, well-plate autosampler, thermostatted column compartment, the Agilent G6430 Triple Quadrupole Mass Spectrometer with an electrospray ionization (ESI) source. Quantitative analysis was carried out using MRM mode. The parameters for MRM transitions are in the Table A.

Table A

MRM	490.2→383.1
Fragmentor	230 V
CE	55 V
Drying Gas Temp	350 °C
Nebulize	40 psi
Drying Gas Flow	10 L/min

[0239] An Agilent XDB-C18, 2.1 x 30 mm, 3.5 μM column was used for the analysis. 5 μL of the samples were injected. Analysis condition: The mobile phase was 0.1% formic acid in water (A) and 0.1% formic acidin methanol (B). The flow rate was 0.4 mL/min. And the gradient of Mobile phase was in the Table B.

Table B

Time	Gradient of Mobile Phase B
0.5 min	5%
1.0 min	95%
2.2 min	95%
2.3 min	5%
5.0 min	stop

[0240] Alternatively, an Agilent 6330 series LC/MS/MS spectrometer equipped with G1312A binary pumps, a G1367A autosampler and a G1314C UV detector were used in the analysis. An ESI source was used on the LC/MS/MS spectrometer. The analysis was done in positive ion mode as appropriate and the MRM transition for each analyte was optimized using standard solution. A Capcell MP-C18 100 x 4.6 mm I.D., 5 μM column (Phenomenex, Torrance, California, USA) was used during the analysis. The mobile phase was 5 mM ammonia acetate, 0.1% MeOH in water (A): 5 mM ammonia acetate, 0.1% MeOH in acetonitrile (B) (70/30, v/v). The flow rate was 0.6 mL/min. Column was maintained at ambient temperature. 20 μL of the samples were injected.

Example A: Compound Stability In Human and Rat Liver Microsomes

[0241] Human or rat liver microsomes incubations were conducted in duplicate in

polypropylene tubes. The typical incubation mixtures consisted of human or rat liver microsomes (0.5 mg protein/mL), compounds of interest (5 μM) and NADPH (1.0 mM) in a total volume of 200 μL potassium phosphate buffer (PBS, 100 mM, pH=7.4). Compounds were dissolved in DMSO and diluted with PBS such that the final concentration of DMSO was 0.05%. The enzymatic reactions were commenced with the addition of protein after a 3-min preincubation and incubated in a water bath open to the air at 37 °C. Reactions were terminated at various time points (0, 5, 10, 15, 30, 60 min) by adding equal volume of ice-cold acetonitrile. The samples were stored at -80 °C until LC/MS/MS assays.

[0242] The concentrations of compounds in the incubation mixtures of human or rat liver microsomes were determined by a LC/MS/MS method. The ranges of the linearity in the concentration range were determined for each tested compounds.

[0243] A parallel incubation was performed using denatured microsomes as the negative control, and reactions were terminated at various time points (0, 15, 60 min) after incubation at 37 °C.

[0244] Dextromethorphan (70 μM) was selected as the positive control, and reactions were terminated at various time points (0, 5, 10, 15, 30, 60 min) after incubation at 37 °C. Both positive and negative control samples were included in each assay to ensure the integrity of the microsomal incubation system.

Data Analysis

[0245] The concentrations of compounds in human or rat liver microsome incubations were plotted as a percentage of the relevant zero time point control for each reaction. The *in vivo* CL_{int} were extrapolated (ref.: Naritomi Y, Terashita S, Kimura S, Suzuki A, Kagayama A, Sugiyama Y. Prediction of human hepatic clearance from in vivo animal experiments and in vitro metabolic studies with liver microsomes from animals and humans. *Drug Metabolism and Disposition* 2001, 29: 1316-1324).

Table 2 Human and rat liver microsomes stability

Example #	Human		Rat	
	$T_{1/2}$ (min)	CL_{int} (mL/min/kg)	$T_{1/2}$ (min)	CL_{int} (mL/min/kg)
Ex. 1	161.6	10.76	97.36	25.51
Ex. 3	144	12.07	50.6	49.09
Ex. 4	112.1	15.51	39.97	62.14
Ex. 5	68.37	25.43	35.71	69.55
Ex. 8	242.6	7.17	74.89	33.16
Ex. 9	∞	N/A	∞	N/A
Ex. 10	527.3	3.30	279.3	8.89
Ex. 13	1129	1.54	95.23	26.08
Ex. 15	503.5	3.45	120.6	20.59
Ex. 16	313.4	5.55	53.67	46.28
Ex. 17	511.8	3.40	279.9	8.87
Ex. 18	212.5	8.18	43.86	56.63
Ex. 19	424.4	4.10	∞	N/A
Ex. 23	∞	N/A	∞	N/A
Ex. 24	∞	N/A	∞	N/A

Example B: Evaluation of Pharmacokinetics After Intravenous and Oral Administration of The Compounds Disclosed Herein In Mice, Rats, Dogs And Monkeys

[0246] The compounds disclosed herein are assessed in pharmacokinetic studies in mice, rats, dogs or monkeys. The compounds are administered as a water solution, 2% HPMC + 1% TWEEN®80 in water solution, 5% DMSO + 5% solutol in saline, 4% MC suspension or capsule. For the intravenous administration, the animals are generally given at 1 or 2 mg/kg dose. For the oral (p.o.) dosing, mice and rats are generally given 5 or 10 mg/kg dose, and dogs and monkeys are generally given 10 mg/kg dose. The blood samples (0.3 mL) are drawn at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12 and 24 h time points or 0.083, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 24 h time points and centrifuged at 3,000 or 4000 rpm for 2 to 10 min. The plasma solutions are collected, stored at -20 °C or -70 °C until analyzed by LC/MS/MS as described above.

Table 3 Pharmacokinetic profiles in rats

Example #	iv dosing					F (%)
	dose (mg/kg)	$T_{1/2}$ (h)	AUC_{last} (ng.h/mL)	Cl/F (L/h/kg)	Vss (L/kg)	
Ex. 1	1	6.39	6541	0.14	1.00	96.0
Ex. 2	2	3.42	20712	0.10	0.22	56.1
Ex. 3	2	3.11	28956	0.07	0.16	61.5
Ex. 5	1	8.74	2551	0.37	2.29	95.6
Ex. 6	1	3.70	2659	0.33	1.25	123.7
Ex. 7	2	3.19	48059	0.04	0.17	95.4
Ex. 8	2	3.02	16596	0.13	0.37	115.1
Ex. 9	1	4.10	7490	0.14	0.37	104.2
Ex. 10	2	4.27	67010	0.03	0.14	79.88
Ex. 11	1	4.92	40399	0.02	0.15	115.8
Ex. 12	2	4.71	411	4.67	18.42	1.3
Ex. 13	1	3.08	11271	0.09	0.32	95.8
Ex. 15	2	3.14	25551	0.08	0.22	97.0
Ex. 16	1	2.65	19399	0.10	0.35	99.77
Ex. 17	1	5.30	38738	0.03	0.17	123.1
Ex. 18	1	2.33	10253	0.10	0.35	97.16
Ex. 19	2	2.58	10075	0.23	0.55	54.66
Ex. 23	1	0.15	561	1.81	0.19	5.9
Ex. 24	2	3.06	8404	0.24	0.55	108

Table 4 Pharmacokinetic profiles in Mice, Dogs and Monkeys

Example #	Species	iv dosing					F (%)
		dose (mg/kg)	$T_{1/2}$ (h)	AUC_{last} (ng.h/mL)	Cl/F (L/h/kg)	Vss (L/kg)	
Ex. 9	Mouse	2	4.02	5329	0.37	0.57	118.7
	Dog	1	0.73	2754	0.37	0.31	44.2
	Monkey	1	3.59	2368	0.45	0.39	27.3

Ex. 15	Mouse	1	2.83	20034	N/A	N/A	116.9
	Dog	1	0.74	2171	0.46	0.37	108.5
	Monkey	1	5.89	3199	0.32	0.76	55.4
Ex. 24	Mouse	2	5.25	96127	0.02	0.14	72.6
	Dog	1	0.57	1840	0.54	0.37	108.5
	Monkey	1	6.05	4642	0.22	0.64	69.8

Example C: Kinase Activity Assay

[0247] The efficacy of the compounds disclosed herein as inhibitors of PI3 kinases and mTOR kinases can be evaluated as follows.

General Description for Kinase Assays

[0248] Kinase assays can be performed by measurement of incorporation ofγ-^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) are coated with MBP (Sigma #M-1891) by incubation of 60 µL/well of 20 µg/mL MBP in Tris-buffered saline (TBS; 50 mM Tris pH 8.0, 138 mM NaCl, 2.7 mM KCl) for 24 h at 4 °C. Plates are washed 3x with 100 µL TBS. Kinase reactions are carried out in a total volume of 34 µL in kinase buffer (5 mM Hepes pH 7.6, 15 mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10 mM $MgCl_2$, 1 mM DTT, 0.02% TritonX-100). Compound dilutions are performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point is measured in duplicate, and at least two duplicate assays are performed for each individual compound determination. Enzyme is added to final concentrations of 10 nM or 20 nM, for example. A mixture of unlabeled ATP andγ-^{33}P ATP is added to start the reaction (2 x 10^6 cpm ofγ-^{33}P ATP per well (3000 Ci/mmole) and 10 µM unlabeled ATP, typically. The reactions are carried out for 1 h at rt with shaking. Plates are washed 7x with TBS, followed by the addition of 50 µL/well scintillation fluid (Wallac). Plates are read using a Wallac Trilux counter. This is only one format of such assays; various other formats are possible, as known to one skilled in the art.

[0249] The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition constant, K_i. The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the condition of the assay. The IC_{50} value is estimated

by preparing a 10 point curve using a ½ log dilution series (for example, a typical curve may be prepared using the following compound concentrations: 10 μM, 3 μM, 1 μM, 0.3 μM, 0.1 μM, 0.03 μM, 0.01 μM, 0.003 μM, 0.001 μM and 0 μM).

PI3 KINASE GENERAL ASSAY PROTOCOL

PI3K (p110α/p85α) (h) [Non-radioactive assay]

[0250] PI3K (p110α/p85α) (h) is incubated in assay buffer containing 10 μM phosphatidylinositol 4,5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the ATP solution. After incubation for 30 minutes at room temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains europium-labelled anti-GST monoclonal antibody, GST-tagged GRP1 PH domain and streptavidin allophycocyanin. The plate is then read in timeresolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula HTRF = 10000 x (Em665nm/Em620nm).

PI3K (p110β/p85α) (h) [Non-radioactive assay]

[0251] PI3K (p110β/p85α) (h) is incubated in assay buffer containing 10 μM phosphatidylinositol-4, 5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 30 minutes at room temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains europium-labelled anti-GST monoclonal antibody, GST-tagged GRP1 PH domain and streptavidin-allophycocyanin. The plate is then read in timeresolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula HTRF = 10000 x (Em665nm/Em620nm).

PI3K (p110δ/p85α) (h) [Non-radioactive assay]

[0252] PI3K (p110δ/p85α) (h) is incubated in assay buffer containing 10 μM phosphatidylinositol-4, 5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 30 minutes at room

temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains europium-labelled anti-GST monoclonal antibody, GST-tagged GRP1 PH domain and streptavidin-allophycocyanin. The plate is then read in timeresolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula HTRF = 10000 x (Em665nm/Em620nm).

PI3K (p120γ) (h) [Non-radioactive assay]

[0253] PI3K (p120γ) (h) is incubated in assay buffer containing 10 μM phosphatidylinositol-4, 5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 30 minutes at room temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains europium-labelled anti-GST monoclonal antibody, GST-tagged GRP1 PH domain and streptavidin-allophycocyanin. The plate is then read in timeresolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula HTRF = 10000 x (Em665nm/Em620nm).

mTOR (h)

[0254] mTOR (h) is incubated with 50 mM HEPES pH 7.5, 1 mM EDTA, 0.01% Tween 20, 2 mg/mL substrate, 3 mM Manganese Chloride and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MnATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 3% phosphoric acid solution. 10 μL of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

[0255] The kinase assays described herein were performed at Millipore UK Ltd, Dundee Technology Park, Dundee DD2 1SW, UK.

[0256] The compounds disclosed herein exhibited potent activities in the PI3Kα(h) and mTOR (h) assays.Table 5 lised the IC_{50}s of some examples described herein in the PI3Kα(h) and mTOR (h) assays.

Table 5 Kinase inhibition data

Example #	IC_{50}(nM)				
	mTOR	PI3K			
		p110α/p85α	p110β/p85α	p110δ/p85α	p120γ
Ex. 1	23	14	/	/	/
Ex. 2	29	6	/	/	/
Ex. 3	16	12	/	/	/
Ex. 4	19	41	/	/	/
Ex. 5	/	17	/	/	/
Ex. 6	/	4	/	/	/
Ex. 7	24	20	/	/	/
Ex. 8	12	6	/	/	/
Ex. 9	9	2	38	2	-
Ex. 10	/	3	/	/	/
Ex. 11	/	8	/	/	/
Ex. 12	/	32	/	/	/
Ex. 15	34	2	27	1	37
Ex. 16	31	2	66	3	5
Ex. 18	/	/	28	2	/
Ex. 19	/	/	28	4	/
Ex.24	3	2	26	3	4

[0257] Alternatively, the kinase activities of the compounds can be measured using KINOME*scan*™, which is based on a competition binding assay that quantitatively measures the ability of a compound to compete with an immobilized, active-site directed ligand. The assay was performed by combining three components: DNA-tagged kinase; immobilized ligand; and a test compound. The ability of the test compound to compete with the immobilized ligand was measured via quantitative PCR of the DNA tag.

[0258] For most assays, kinase-tagged T7 phage strains were prepared in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage and incubated with shaking at 32 °C until lysis. The lysates were centrifuged and filtered to remove

cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SEABLOCK™ (Pierce), 1% BSA, 0.05% TWEEN®20, 1 mM DTT) to remove unbound ligand and to reduce nonspecific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SEABLOCK™, 0.17x PBS, 0.05% TWEEN®20, 6 mM DTT). All reactions were performed in polystyrene 96-well plates in a final volume of 0.135 mL. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% TWEEN®20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% TWEEN®20, 0.5 μM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

[0259] The kinase assays described herein were performed using KINOME*scan*™ Profiling Service at DiscoveRx Corporation, 42501 Albrae St. Fremont, CA 94538, USA.

Example D: Tumor Xenograft Models

[0260] The efficacy of compounds disclosed herein was evaluated in a standard murine model of tumorigenesis. Human tumor cells (U87MG glioblastoma cells from ATCC) were expended in culture, harvested, and injected subcutaneously onto the rear flank of 6-7 week old female athymic nude mice (BALB/cA nu/nu, Hunan SLAC Laboratory Animal, Co.) (n = 6-10 for vehicle group and for each dosing group). When tumors reached a volume of 100-250 mm^3, animals were randomly divided into vehicle control (for example, 5% DMSO+70% Captisol® (30%), 7% HCl (pH1), 18% Captisol® (30%); or 7% DMSO, 7% HCl (pH1), 70% Captisol® (30%), 16% Captisol® (30%), or the like) and compound groups. Subsequent administration of compound by oral gavage begins anywhere from day 0 to day 15 post tumor cell challenge and generally continues with once a day for the duration of the experiment.

Tumor Growth Inhibition (TGI) Analysis

[0261] Progression of tumor growth is assessed by tumor volumes and recorded as a function of time. The long (L) and short (W) axes of the subcutaneous tumors were measured

with calipers twice weekly, and the tumor volume (TV) calculated as (L x W^2)/2). TGI was calculated from the difference between the median tumor volumes of vehicle-treated and drug-treated mice, expressed as a percentage of the median tumor volume of the vehicle-treated control group, by the following relation:

$$\%TGI = \left(\frac{\text{Median Tumor Volume}_{control} - \text{Median Tumor Volume}_{drug\text{-}treated}}{\text{Median Tumor Volume}_{control}} \right) \times 100$$

[0262] Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe psot hoc testing for multiple comparisons. Vehicle alone (5% DMSO+70% Captisol® (30%), 7% HCl (pH1), 18% Captisol® (30%); or 7% DMSO, 7% HCl (pH1), 70% Captisol® (30%), 16% Captisol® (30%), or the like) is the negative control.

Table 6 Selected results from tumor xenograft model (U87MG) studies

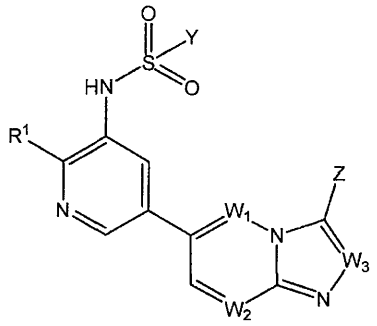
Example #	**Dosing (mg/kg)**	**TGI (%)**
		U87MG
Ex. 2 14 days	1	6
	3	21
	10	35
Ex. 6 12 days	0.3	14
	1	41
	3	71
Ex. 9 12 days	1	23
	3	26
	10	62
Ex. 10 12 days	1	32
	3	44
	10	65
Ex. 15 12 days	3	28
	10	51
Ex. 16 12 days	3	14
	10	43

Ex. 24 9 days	0.3	53
	1	84
	3	108

[0263] Finally, it should be noted that there are alternative ways of implementing the present invention. Accordingly, the present embodiments are to be considered as illustrative and not restrictive and the invention is not be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims. All publications and patents cited herein are incorporated by reference.

What is claimed is:

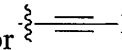
1. A compound of Formula (I):



(I),

or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a solvate or a pharmaceutically acceptable salt thereof, wherein:

each of W_1, W_2 and W_3 is independently N or CR^c;

Z is CN, N_3 or ;

X is H, D, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl or -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl and -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl and $(C_2$-$C_6)$alkynyl;

Y is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl;

R^1 is H, D, Cl, OR^a, NR^aR^b, $(C_1$-$C_6)$aliphatic or $(C_3$-$C_6)$cycloalkyl, wherein each of the $(C_1$-$C_6)$aliphatic and $(C_3$-$C_6)$cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OR^a, SR^a and NR^aR^b, provided that when each of

W_1, W_2 and W_3 is CH, R^1 is not H or NH_2;

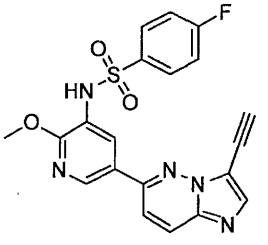
each R^a and R^b is independently H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, -$(C_1\text{-}C_4)$alkylene-$(C_6\text{-}C_{10})$aryl or -$(C_1\text{-}C_4)$alkylene-(5-10 membered heteroaryl); or when R^a and R^b are bonded to the same nitrogen atom, R^a and R^b, together with the nitrogen atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered heterocyclic ring, wherein each of the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OH, NH_2, $(C_1\text{-}C_6)$alkoxy, and $(C_1\text{-}C_6)$alkylamino; and

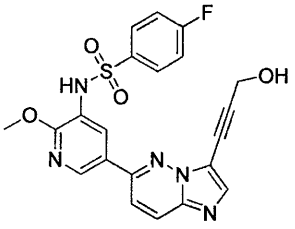
each R^c is independently H.

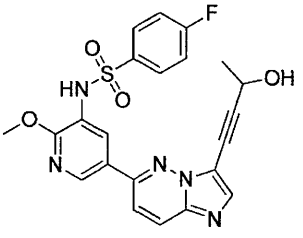
2. The compound according to claim 1, wherein each of W_1 and W_2 is independently N or CR^c, W_3 is CR^c.

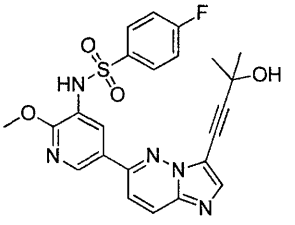
3. The compound according to claim 1, wherein R^1 is H, D, Cl, CH_3, CH_2CH_3, CF_3, CH_2CF_3, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$, provided that when each of W_1, W_2 and W_3 is CH, R^1 is not H or NH_2.

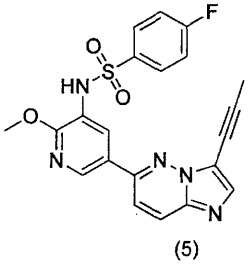
4. The compound according to claim 1 having one of the following structures:

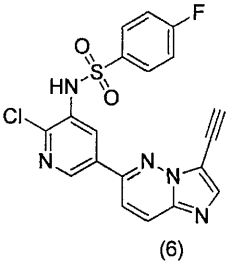

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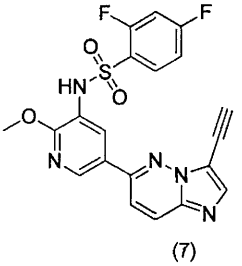

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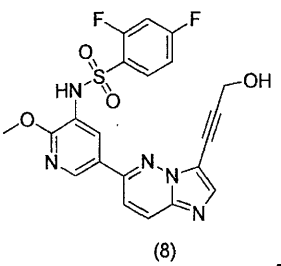

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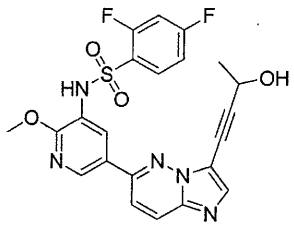

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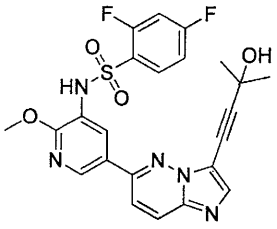

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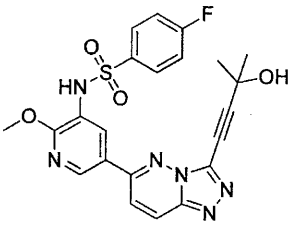

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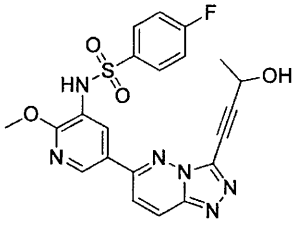
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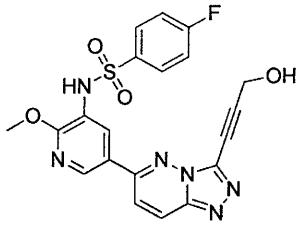
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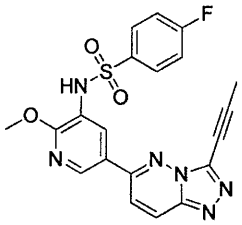
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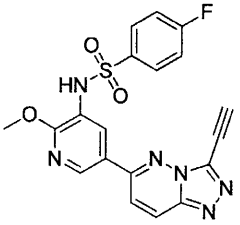
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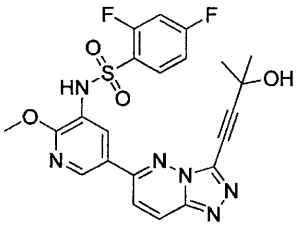
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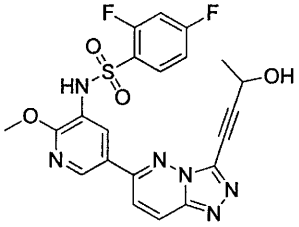
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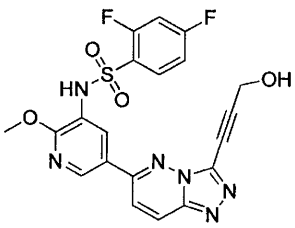
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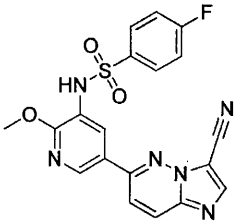
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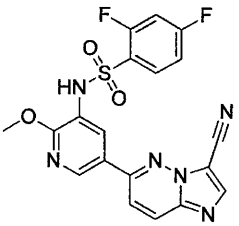
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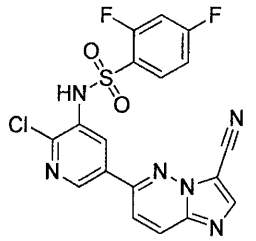
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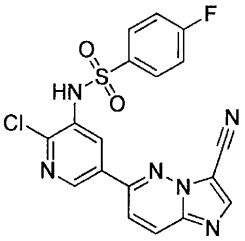
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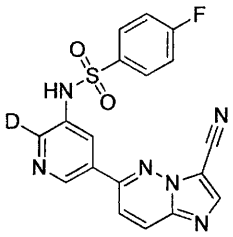
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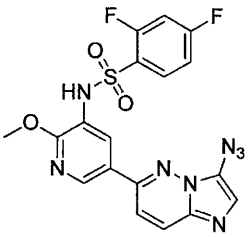
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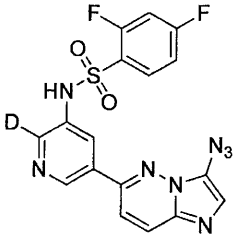
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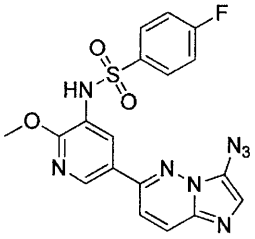
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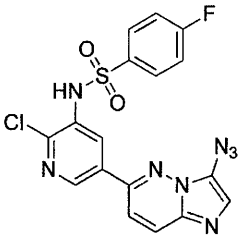
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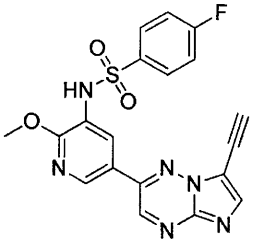
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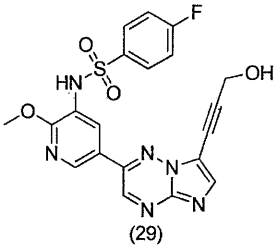
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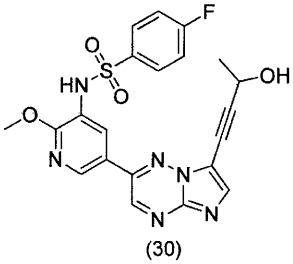
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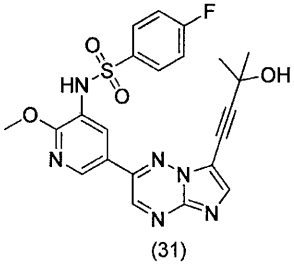
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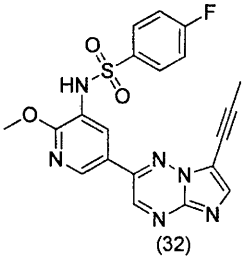
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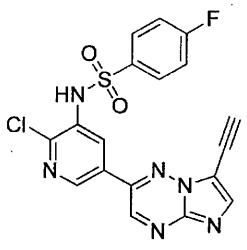
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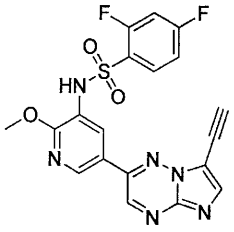
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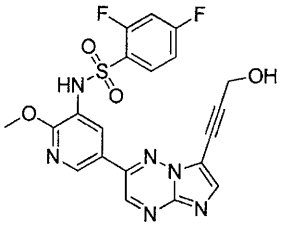
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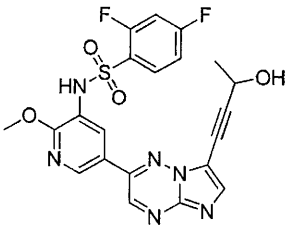
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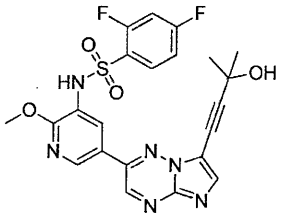
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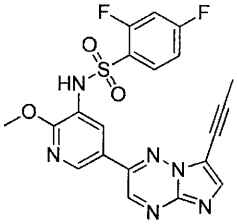
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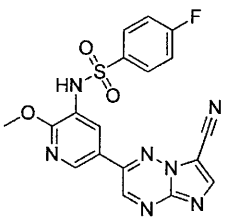
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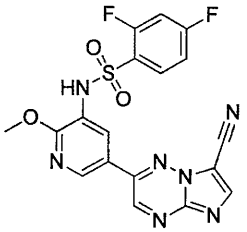
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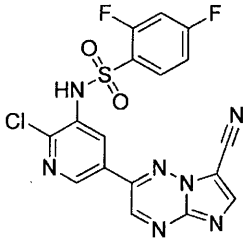
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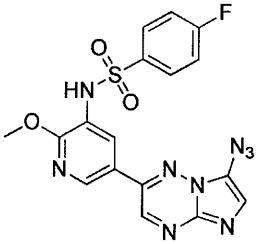
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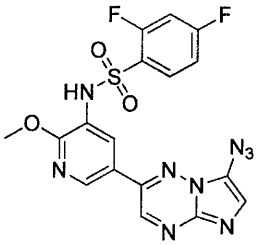
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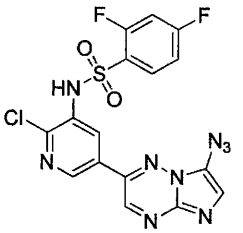
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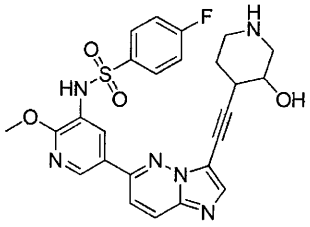
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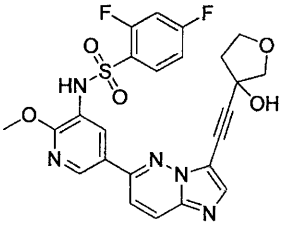
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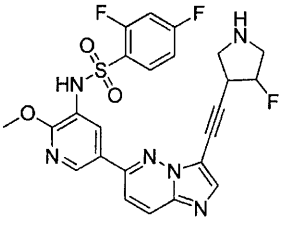
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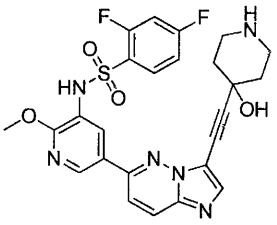
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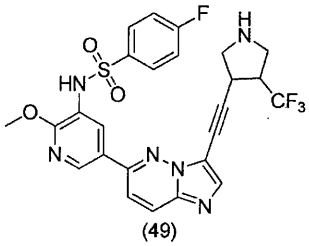
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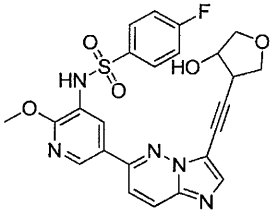
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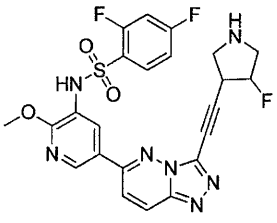
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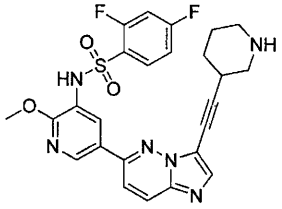
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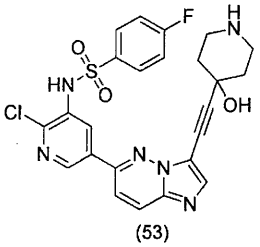
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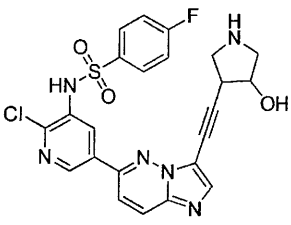
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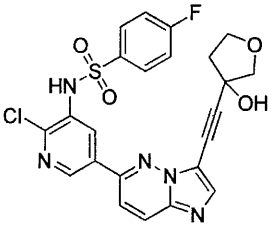
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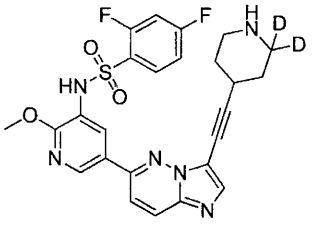
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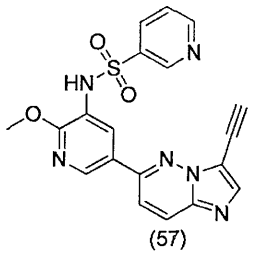
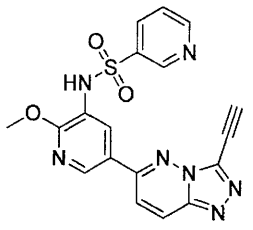
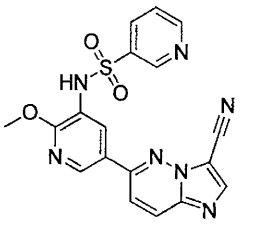
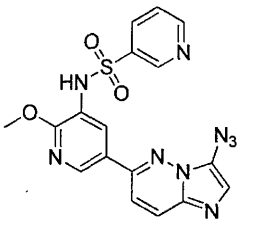
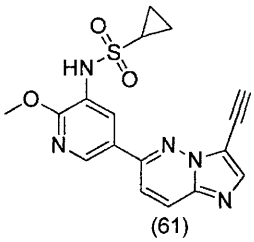
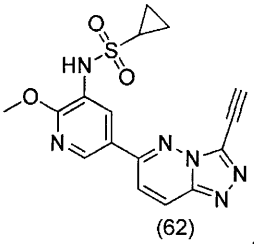
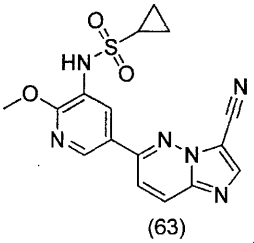
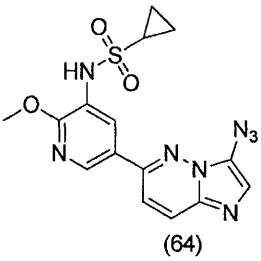
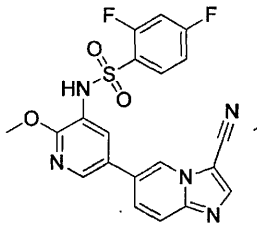
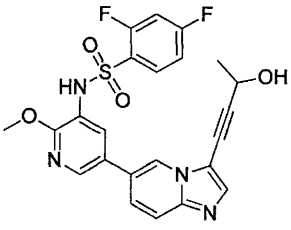
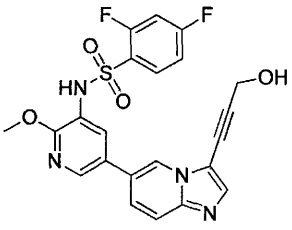
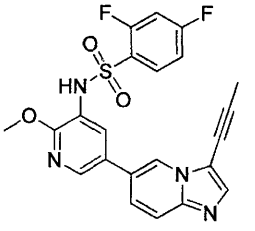
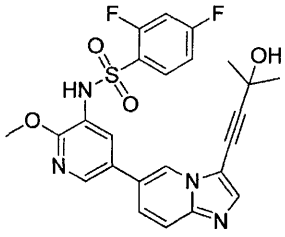
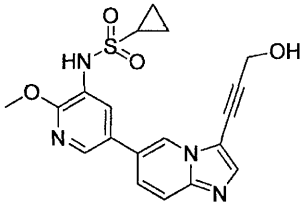
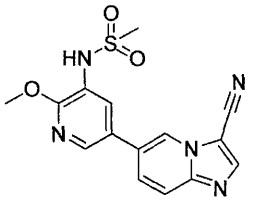
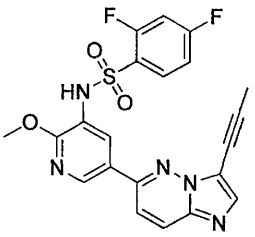
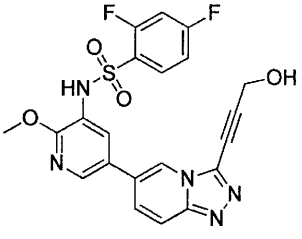
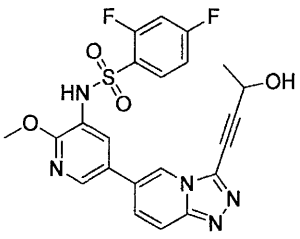
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5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

6. The pharmaceutical composition according to claim 5, further comprising an additional therapeutic agent selected from a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis or a combination thereof.

7. The pharmaceutical composition according to claim 6, wherein the additional therapeutic agent is chlorambucil, melphalan, cyclophosphamide, ifosfamide, busulfan, carmustine, lomustine, streptozocin, cisplatin, carboplatin, oxaliplatin, dacarbazine, temozolomide, procarbazine, methotrexate, fluorouracil, cytarabine, gemcitabine, mercaptopurine, fludarabine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, topotecan, irinotecan, etoposide, trabectedin, dactinomycin, doxorubicin, epirubicin, daunorubicin, mitoxantrone, bleomycin, mitomycin, ixabepilone, tamoxifen, flutamide, gonadorelin analogues, megestrol, prednidone, dexamethasone, methylprednisolone, thalidomide, interferon alfa, leucovorin, sirolimus, temsirolimus, everolimus, afatinib, alisertib, amuvatinib, apatinib, axitinib, bortezomib, bosutinib, brivanib, cabozantinib, cediranib, crenolanib, crizotinib, dabrafenib, dacomitinib, danusertib, dasatinib, dovitinib, erlotinib, foretinib, ganetespib, gefitinib, ibrutinib, icotinib, imatinib, iniparib, lapatinib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, nilotinib, niraparib, oprozomib, olaparib, pazopanib, pictilisib, ponatinib, quizartinib, regorafenib, rigosertib, rucaparib, ruxolitinib, saracatinib, saridegib, sorafenib, sunitinib, tasocitinib, telatinib, tivantinib, tivozanib, tofacitinib, trametinib, vandetanib, veliparib, vemurafenib, vismodegib, volasertib, alemtuzumab, bevacizumab, brentuximab vedotin, catumaxomab, cetuximab, denosumab, gemtuzumab, ipilimumab, nimotuzumab, ofatumumab, panitumumab, ramucirumab, rituximab, tositumomab, trastuzumab, or a combination thereof.

8. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for preventing, managing, treating or lessening the severity of a proliferative disorder, wherein the proliferative disorder is colon cancer, breast cancer, lung cancer, or prostate cancer.