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(54) Title: PI3 KINASE MODULATORS AND METHODS OF USE

(57) Abstract: This invention relates to the field of lipid kinases and modulators thereof. In particular, the invention relates to modulators of phosphatidylinositol 3-kinases (PI3 kinases or PBKs) signaling pathways, and methods of their use. The invention also provides pharmaceutically acceptable compositions comprising such compounds and methods of using the compositions in modulating of PI3K signaling pathways and their related disorders in mammals, especially humans.



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 61/676,966, filed on July 29, 2012, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

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

BACKGROUND

[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 messages 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). Phosphorylated 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 calcium/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 (PI3K α , PI3K β , PI3K γ and PI3K δ) comprises heterodimers between a p110 catalytic subunit (p110 α , p110 β , p110 γ and p110 δ respectively), and a p85 regulatory adapter subunits (i.e., p85 α , p85 β , p55 δ , p55 α and p50 α). 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 p110 α , 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 et al., *Breast Cancer Res. Treat* **2006**, 96, 91-95; Saal et al., *Cancer Res.* **2005**, 65, 2554-2559; Samuels et al., *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., *Oncogene* **2005**, 24, 1477-1480), hepatocellular carcinoma (Lee et al., id), small and non-small cell lung cancer (Tang et al., *Lung Cancer* **2006**, 11, 181-191; Massion et al., *Am J Respir Crit Care Med* **2004**, 170, 1088-1094), thyroid carcinoma (Wu et al., *J Clin Endocrinol Metab* **2005**, 90, 4688-4693), acute myelogenous leukemia (AML) (Sujobert et al., *Blood* **1997**, 106, 1063-1066), chronic myelogenous leukemia (CML) (Hickey et al., *J Biol Chem* **2006**, 281, 2441-2450), and glioblastomas (Hartmann et al., *Acta Neuropathol (Berl)* **2005**, 109, 639-642).

[007] mTOR is a highly conserved serine-threonine kinase with lipid kinase activity and participates 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 availability 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 rapamycin and its analogues such as temsirolimus (CCI-779) and everolimus (RAD001). Rapamycin was found to

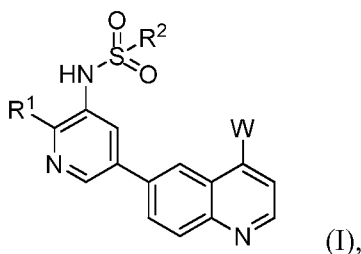
inhibit mTOR and thereby induce G1 arrest and apoptosis. The mechanism of rapamycin growth inhibition was found to be related to formation of complexes of rapamycin with FK-binding protein 12 (FKBP-12). These complexes then bound with high affinity to mTOR, preventing activation and resulting in inhibition 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 Administration for the treatment certain types of cancer.

[009] In view of the important role of PI3Ks and mTOR in biological processes and disease states, inhibitors of these kinases are desirable (“Phosphatidylinositol 3-kinase isoforms as a novel drug targets.” *Current Drug Targets*, **2011**, 12, 1056-1081; “Progress in the preclinical discovery 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 invention provides compounds that inhibit, regulate, and/or modulate PI3K or mTOR, and are useful in the treatment of hyperproliferative diseases, such as cancer in humans. This invention also provides methods of making the compound, methods of using such compounds in the treatment of hyperproliferative diseases in humans and pharmaceutical compositions containing such compounds.

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



or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, wherein each R^1 , R^2 and W is as defined herein.

[012] In certain embodiments, W is D, CN, N_3 , C_{5-12} spirobicycyl or $\text{---}\equiv\text{X}$; wherein the C_{5-12} spirobicycyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3 , $-\text{OR}^a$, $-\text{SR}^a$ and $-\text{NR}^a\text{R}^b$;

X is H, D, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N₃, C₁₋₄alkyl, -OR^a, -SR^a and -NR^aR^b;

R¹ is H, D, Cl, -OR^a, C₁₋₆alkyl or C₃₋₆cycloalkyl, wherein each of the C₁₋₆alkyl and C₃₋₆cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, -OR^a, -SR^a and -NR^aR^b;

R² is C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N₃, -OR^a, -SR^a and -NR^aR^b; and

each R^a and R^b is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), -(C₁₋₄alkylene)-(C₆₋₁₀aryl) or -(C₁₋₄alkylene)-(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.

[013] In another embodiment, W is CN, C₅₋₁₂spirobicyclyl or $\left\{ \begin{array}{c} \diagup \\ \diagdown \end{array} \right\} \equiv \text{X}$, wherein the C₅₋₁₂spirobicyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, -OR^a, -SR^a and -NR^aR^b.

[014] In another embodiment, X is H, D, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, C₁₋₃alkyl, -OR^a and -NR^aR^b.

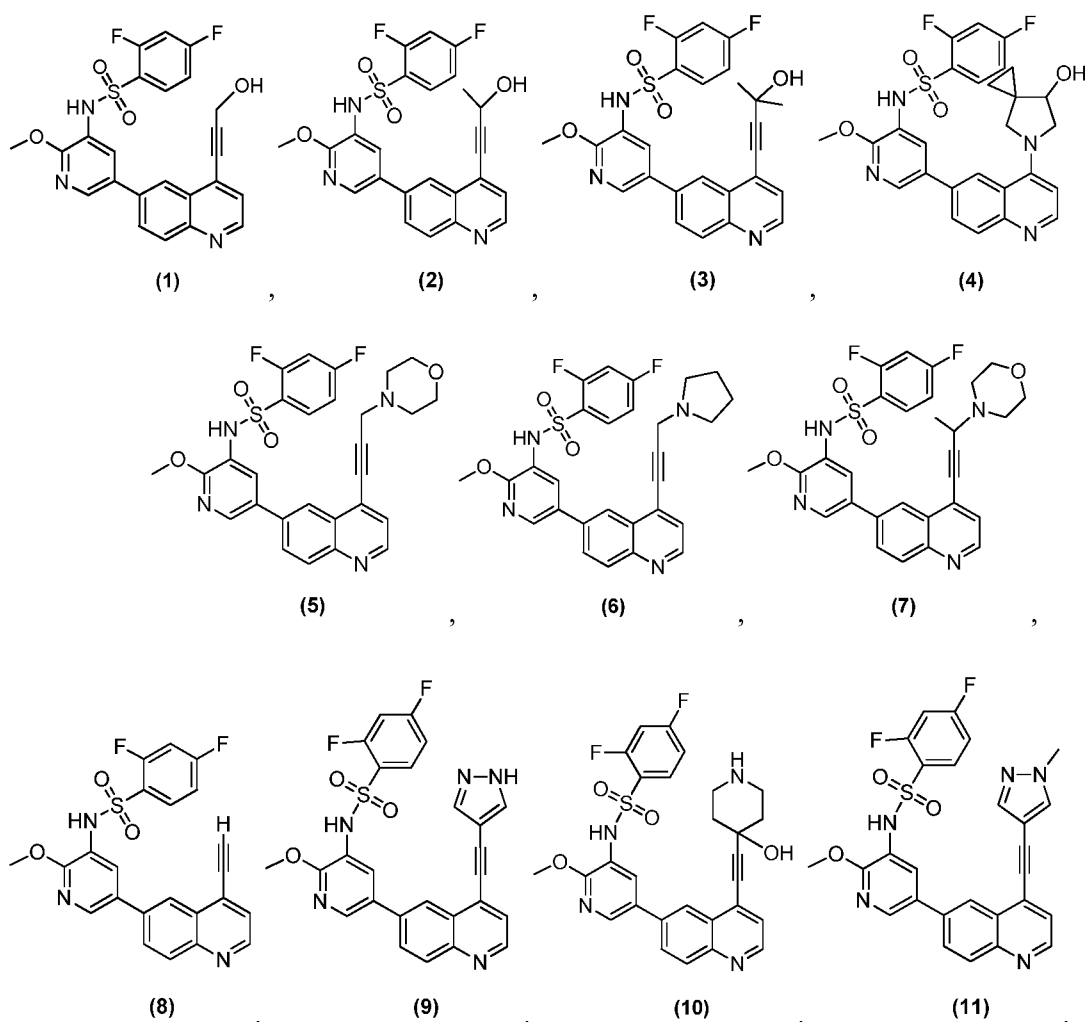
[015] In another embodiment, R¹ is H, D, Cl or -OR^a.

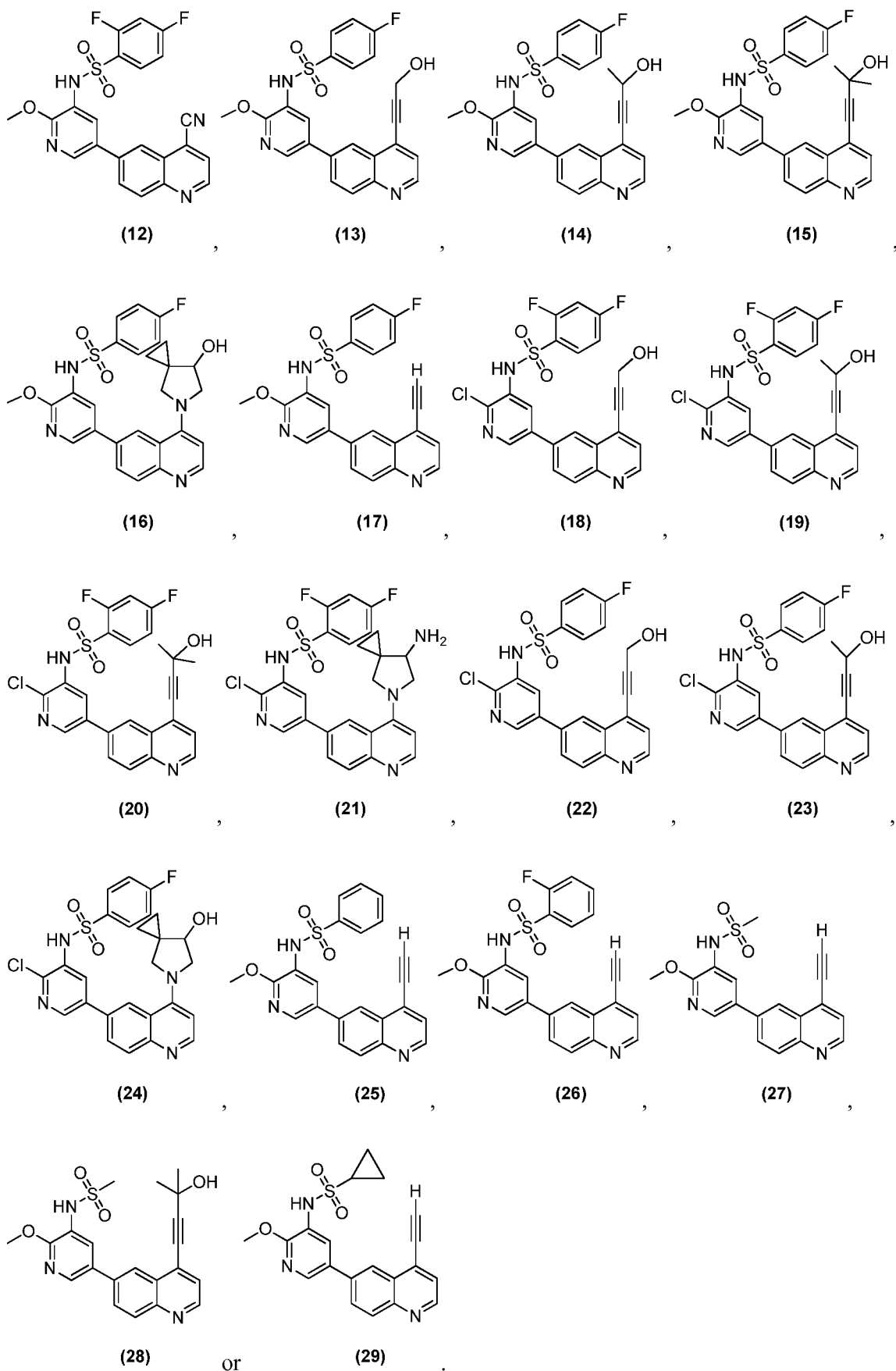
[016] In another embodiment, R^2 is C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{6-10} aryl, wherein each of the C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{6-10} aryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F and Cl.

[017] In another embodiment, R^1 is Cl or OMe.

[018] In another embodiment, each R^a and R^b is independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, $-(C_{1-2}$ alkylene)-(C_{3-6} heterocyclyl), $-(C_{1-2}$ alkylene)-(C_{6-10} aryl) or $-(C_{1-2}$ 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.

[019] Some non-limiting examples of the compounds disclosed herein, and their pharmaceutically acceptable salts and solvates thereof, are shown in the following:





[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 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, prednisone, 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, tosimumab, 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 administering 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 herein is 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 comprises contacting the receptor with the compound according to the present invention, or with the pharmaceutical 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, wherein the method comprises contacting the cell with an effective proliferative inhibiting amount of the compound disclosed herein or the pharmaceutical composition disclosed herein. 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, wherein the method comprises administering to the patient in need of such treatment an effective therapeutic amount of the compound disclosed herein or the pharmaceutical composition disclosed herein. In some embodiments, the method further comprises administering an additional therapeutic agent.

[030] In another aspect, provided herein is a method of inhibiting tumor growth in a patient,

the method comprises administering to the patient in need thereof an effective therapeutic amount of the compound disclosed herein or the pharmaceutical composition disclosed herein. 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 disclosed herein 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] 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 Sorrell et al., "Organic Chemistry" University Science Books, Sausalito: **1999**, and Smith et al., "March's Advanced Organic Chemistry", John Wiley & Sons, New York: **2007**, all of which are incorporated hereby by reference.

[035] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as those illustrated 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" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. 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. Examples of substituent include, but are not limited to, D, F, Cl, CN, N₃, alkyl, haloalkyl, alkenyl, alkynyl, OH, SH, NH₂, alkoxy, alkylthio, arylamino and alkylamino.

[036] The term "alkyl" or "alkyl group" refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twenty carbon atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. Unless otherwise specified, alkyl groups contain 1-20 carbon atoms. In some embodiments, alkyl groups contain 1-8 carbon atoms. In other embodiments, alkyl groups contain 1-6 carbon atoms. In still other embodiments, alkyl groups contain 1-4 carbon atoms, and in yet other embodiments, alkyl groups contain 1-3 carbon atoms.

[037] Some non-limiting examples of alkyl groups include methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (*n*-Pr, *n*-propyl, -CH₂CH₂CH₃), 2-propyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-butyl (*n*-Bu, *n*-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (*s*-Bu, *s*-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (*n*-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), 1-heptyl, 1-octyl, and the like.

[038] The terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched saturated carbon chain.

[039] The term "alkylene", refers to a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described herein. Some non-limiting examples include methylene (-CH₂-), ethylidene (-CH(CH₃)-), ethylene (-CH₂CH₂-), isopropylene (-CH(CH₃)CH₂-), and the like.

[040] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to twelve carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp² 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. Some non-limiting examples include ethylenyl or vinyl ($-\text{CH}=\text{CH}_2$), allyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), and the like.

[041] The term "alkynyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to twelve 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. Some non-limiting examples include ethynyl ($-\text{C}\equiv\text{CH}$), propynyl (propargyl, $-\text{CH}_2\text{C}\equiv\text{CH}$), $-\text{C}\equiv\text{C}-\text{CH}_3$, and the like.

[042] The term "alkoxy" 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 1-8 carbon atoms. In other embodiments, alkoxy groups contain 1-6 carbon atoms. In still other embodiments, alkoxy groups contain 1-4 carbon atoms, and in yet other embodiments, alkoxy groups contain 1-3 carbon atoms.

[043] Some non-limiting examples of alkoxy groups include methoxy (MeO , $-\text{OCH}_3$), ethoxy (EtO , $-\text{OCH}_2\text{CH}_3$), 1-propoxy ($n\text{-PrO}$, *n*-propoxy, $-\text{OCH}_2\text{CH}_2\text{CH}_3$), 2-propoxy (*i*-PrO, *i*-propoxy, $-\text{OCH}(\text{CH}_3)_2$), 1-butoxy ($n\text{-BuO}$, *n*-butoxy, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-methyl-1-propoxy (*i*-BuO, *i*-butoxy, $-\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 2-butoxy (*s*-BuO, *s*-butoxy, $-\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 2-methyl-2-propoxy (*t*-BuO, *t*-butoxy, $-\text{OC}(\text{CH}_3)_3$), 1-pentoxy (*n*-pentoxy, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-pentoxy ($-\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$), 3-pentoxy ($-\text{OCH}(\text{CH}_2\text{CH}_3)_2$), 2-methyl-2-butoxy ($-\text{OC}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$), 3-methyl-2-butoxy ($-\text{OCH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$), 3-methyl-1-butoxy ($-\text{OCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2-methyl-1-butoxy ($-\text{OCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), and the like.

[044] The term "alkylthio" or "alkythio" refers to an alkyl group, as previously defined, attached to the principal carbon atom through a sulfur atom. Unless otherwise specified, alkylthio groups contain 1-20 carbon atoms. In some embodiments, alkylthio groups contain 1-8 carbon atoms. In other embodiments, alkylthio groups contain 1-6 carbon atoms. In still other embodiments, alkylthio groups contain 1-4 carbon atoms, and in yet other embodiments, alkylthio groups contain 1-3 carbon atoms.

[045] The terms "haloalkyl" or "haloalkoxy" refers to alkyl, or alkoxy, as the case may be, substituted with one or more halogen atoms. Some non-limiting examples include $-\text{CF}_3$, $-\text{OCF}_3$, and the like.

[046] 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 one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable alkylamino radicals may be mono or dialkylamino such as *N*-methyldamino, *N*-ethyldamino, *N,N*-dimethyldamino, *N,N*-diethyldamino, and the like.

[047] The term "aryldamino" refers to amino groups substituted with one or two aryl radicals, such as *N*-phenyldamino. The aryldamino radical may be further substituted with one or more substituents described herein on the aryl ring portion of the radical.

[048] The term "aminoalkyl" refers to 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 aminoheyl.

[049] The term "carbocycle", "carbocyclyl", "carbocyclic ring" or "cycloaliphatic" refers 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. Some non-limiting examples of suitable cycloaliphatic groups include cycloalkyl, cycloalkenyl, and cycloalkynyl. Further examples of cycloaliphatic groups include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, and the like. The term "cycloalkyl" refers to a monovalent or multivalent saturated ring having 3 to 12 carbon atoms as a monocyclic ring system. The cycloalkyl groups herein are optionally substituted independently with one or more substituents described herein.

[050] The term "heterocycle", "heterocyclyl" or "heterocyclic ring" as used interchangeably herein refers to a monocyclic, bicyclic, or tricyclic ring system in which one or more ring members are an independently selected heteroatom and that is completely saturated or that contains one or more units of unsaturation, but not aromatic, having a single point of attachment to the rest of the molecule. One or more ring atoms are optionally substituted independently with one or more substituents described herein. In some embodiments, the "heterocycle", "heterocyclyl", or "heterocyclic ring" group is a monocycle having 3 to 8 ring members (2 to 7 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S, wherein S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, PO or PO₂ 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 SO₂, PO or PO₂.

[051] The heterocyclyl may be a carbon radical or heteroatom radical. Some non-limiting examples of heterocyclic rings include pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homo-piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 2-pyrroliny, 3-pyrroliny, indoliny, 2*H*-pyranyl, 4*H*-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, and 1,2,3,4-tetrahydro iso-quinoliny. Examples of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidindionyl and 1, 1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

[052] The term "heteroatom" refers to 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).

[053] The term "halogen" refers to F, Cl, Br or I.

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

[055] The term "D" or "²H" refers to a single deuterium atom. One of this radical may be attached, for example, to a methyl group to form a mono-deuterated methyl group (-CDH₂), two of deuterium atoms may be attached to a methyl group to form a di-deuterated methyl (-CD₂H), and three of deuterium atoms may be attached to a methyl group to form a tri-deuterated methyl group (-CD₃).

[056] The term "N₃" refers to an azide moiety. This radical may be attached, for example, to a methyl group to form azidomethane (methyl azide, MeN₃); or attached to a phenyl group to form phenyl azide (PhN₃).

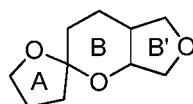
[057] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy" or "aryloxyalkyl" refers to monocyclic, bicyclic, and tricyclic carbocyclic ring systems having a total of six to fourteen ring members, wherein at least one ring in the system is aromatic, wherein each ring in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

the rest of the molecule. The term "aryl" may be used interchangeably with the term "aryl ring". Examples of aryl rings would include phenyl, naphthyl, and anthracene. The aryl groups herein are optionally substituted independently with one or more substituents described herein.

[058] 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 five to fourteen 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 5-7 ring members and that has a single point of attachment to the rest of the molecule. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic". The heteroaryl groups herein are optionally substituted independently with one or more substituents described herein.

[059] Some 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, 4-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, quinoliny (e.g., 2-quinoliny, 3-quinoliny, 4-quinoliny), and isoquinoliny (e.g., 1-isoquinoliny, 3-isoquinoliny or 4-isoquinoliny).

[060] The term "spirocyclyl", "spirocyclic", "spiro bicycyl" or "spiro bicyclic" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted 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 bicycyl". Each cyclic ring in a spirocyclyl group is a carbocyclic or a heterocyclic.



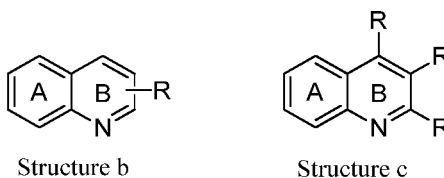
Structure a

[061] The term "unsaturated" as used herein, refers to that a moiety has one or more units of

unsaturation.

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

[063] As described herein, a bond drawn from a substituent to the center of one ring within a ring system (as shown below) represents substitution of the substituent at any substitutable position on the rings to which it is attached. For example, Structure b represents possible substitution in any of the positions on the B ring shown in Structure c.



[064] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, 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. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention.

[065] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. 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.

[066] Unless otherwise stated, all tautomeric forms of the compounds of the invention 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.

[067] The term "prodrug" refers to 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 of the invention may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic C₁₋₂₄ esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound of the invention 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 Higuchi et al., *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, Roche et al., ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, **1987**; Rautio et al., *Prodrugs: Design and Clinical Applications*, *Nature Reviews Drug Discovery*, **2008**, 7, 255-270, and Hecker et al., *Prodrugs of Phosphates and Phosphonates*, *J Med. Chem.*, **2008**, 51, 2328-2345, all of which are incorporated herein by reference.

[068] 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 compounds of the invention, 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.

[069] Stereochemical definitions and conventions used herein generally follow Parker et al., ed., *McGraw-Hill Dictionary of Chemical Terms* (**1984**) McGraw-Hill Book Company, New York; and Eliel et al., *"Stereochemistry of Organic Compounds"*, John Wiley & Sons, Inc., New York, **1994**. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. 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. The term "racemic mixture" or "racemate"

refers to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[070] A "pharmaceutically acceptable salt" as used herein, refers to organic or inorganic salts of a compound of the invention. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmacol Sci.* **1977**, 66, 1-19, which is incorporated herein by reference. Some non-limiting examples of pharmaceutically acceptable, nontoxic salts include 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 $N^+(C_{1-4} \text{ alkyl})_4$ 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.

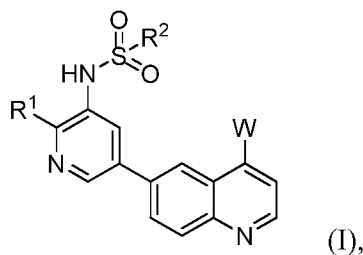
[071] A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine. The term "hydrate"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

[072] 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 $-\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl) ethoxy-methyl, 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 Greene et al., *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, **1991** and Kocienski et al., *Protecting Groups*, Thieme, Stuttgart, **2005**.

DESCRIPTION OF COMPOUNDS OF THE INVENTION

[073] The present invention provides quinoline 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):



or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, wherein each R^1 , R^2 and W is as defined herein.

[074] In certain embodiments, W is D, CN, N_3 , C_{5-12} spirobicycyl or $\text{---}\text{X}$; wherein the C_{5-12} spirobicycyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3 , $-\text{OR}^a$, $-\text{SR}^a$ and $-\text{NR}^a\text{R}^b$;

X is H, D, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl, $-(\text{C}_{1-4}\text{alkylene})-(\text{C}_{3-6}\text{cycloalkyl})$, $-(\text{C}_{1-4}\text{alkylene})-(\text{C}_{3-6}\text{heterocyclyl})$ or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl, $-(\text{C}_{1-4}\text{alkylene})-(\text{C}_{3-6}\text{cycloalkyl})$, $-(\text{C}_{1-4}\text{alkylene})-(\text{C}_{3-6}\text{heterocyclyl})$ 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 , C_{1-4} alkyl, $-\text{OR}^a$, $-\text{SR}^a$ and

-NR^aR^b;

R¹ is H, D, Cl, -OR^a, C₁₋₆alkyl or C₃₋₆cycloalkyl, wherein each of the C₁₋₆alkyl and C₃₋₆cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, -OR^a, -SR^a and -NR^aR^b;

R² is C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N₃, -OR^a, -SR^a and -NR^aR^b; and

each R^a and R^b is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), -(C₁₋₄alkylene)-(C₆₋₁₀aryl) or -(C₁₋₄alkylene)-(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.

[075] In another embodiment, W is CN, C₅₋₁₂spirobicyclyl or $\text{---}\text{X}$, wherein the C₅₋₁₂spirobicyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, -OR^a, -SR^a and -NR^aR^b.

[076] In another embodiment, X is H, D, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, C₁₋₃alkyl, -OR^a and -NR^aR^b.

[077] In another embodiment, R¹ is H, D, Cl or -OR^a.

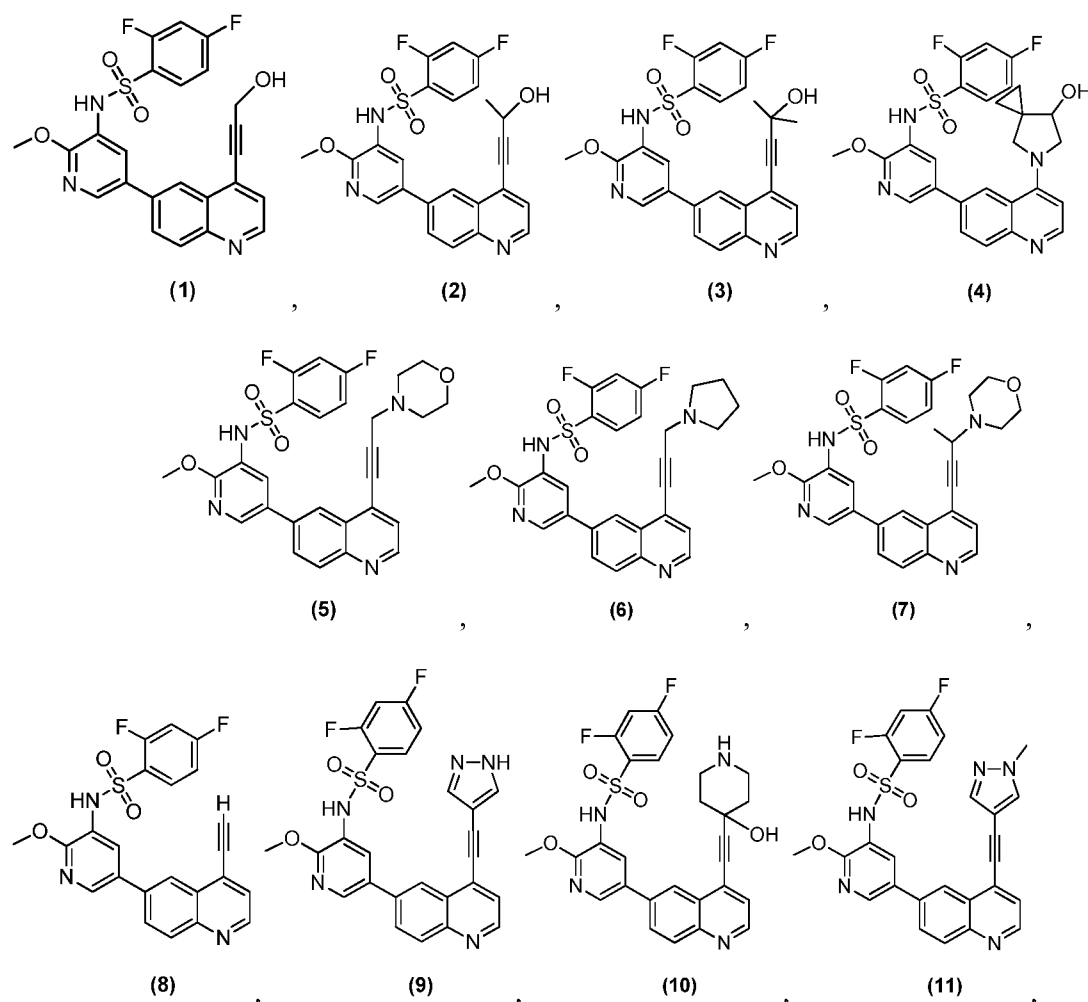
[078] In another embodiment, R² is C₁₋₆alkyl, C₃₋₆cycloalkyl or C₆₋₁₀aryl, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl and C₆₋₁₀aryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F and Cl.

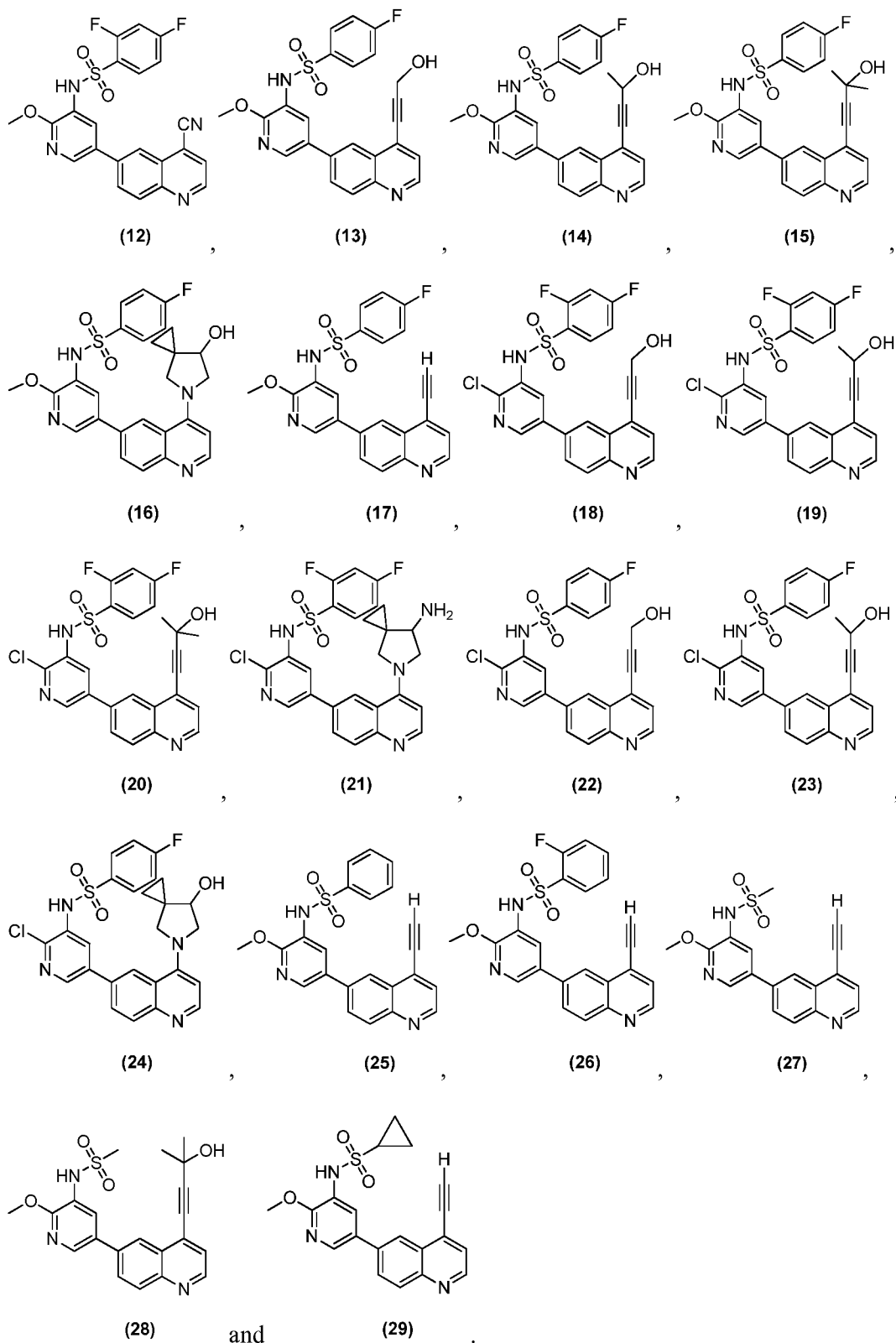
[079] In another embodiment, R¹ is Cl or OMe.

[080] In another embodiment, each R^a and R^b is independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, $-(C_{1-2}$ alkylene)-(C_{3-6} heterocyclyl), $-(C_{1-2}$ alkylene)-(C_{6-10} aryl) or $-(C_{1-2}$ 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.

[081] Some non-limiting examples of the compounds disclosed herein, and their pharmaceutically acceptable salts and solvates thereof, include:

Table 1





[082] The present invention also comprises the use of a compound of the invention, 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 of the present invention are useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of PI3K or mTOR. 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.

[083] 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).

[084] Unless otherwise stated, all stereoisomers, geometric isomers, tautomers, solvates, metabolites, salts, and pharmaceutically acceptable prodrugs of the compounds of the invention are within the scope of the invention.

[085] 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.

[086] The compounds of the invention also 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).

[087] The desired salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

COMPOSITION, FORMULATIONS AND ADMINISTRATION OF COMPOUNDS OF THE INVENTION

[088] 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 of the invention is such that is effective to detectably inhibit a protein kinase in a biological sample or in a patient.

[089] It will also be appreciated that certain of the compounds of present invention 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 adducts or derivatives 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.

[090] As described above, the pharmaceutically acceptable compositions of the present 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. Troy et al., *Remington: The Science and Practice of Pharmacy*, 21st, **2005**, Lippincott Williams & Wilkins, Philadelphia and Swarbrick et al., *Encyclopedia of Pharmaceutical Technology*, eds. **1988-1999**, Marcel Dekker, New York, all of which are herein incorporated by reference in their entireties, 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 of the invention 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.

[091] Some non-limiting examples of materials which can serve as pharmaceutically acceptable carriers include 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.

[092] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" 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.

[093] 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 TWEEN[®], SPAN[®] 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.

[094] Some non-limiting examples of the pharmaceutically acceptable compositions of this

invention may be orally administered in any orally acceptable dosage form including 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.

[095] 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.

[096] 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.

[097] 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. Some non-limiting examples of carriers for topical administration of the compounds of this invention include 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. Some non-limiting examples of suitable carriers include mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[098] 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.

[0099] Some non-limiting examples of liquid dosage forms for oral administration include 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.

[0100] 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.

[0101] 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 of the present invention, 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.

[0102] 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. Examples 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.

[0103] 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.

[0104] 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, polyvinylpyrrolidone, 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.

[0105] 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. Examples 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 polyethylene glycols and the like.

[0106] 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. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0107] 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.

[0108] The compounds of the invention 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 of the present invention 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.

[0109] 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.

[0110] 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.

[0111] For example, chemotherapeutic agents or other antiproliferative agents may be combined with the compounds of this invention to treat proliferative disease or cancer. Some non-limiting examples chemotherapeutic agents or other antiproliferative agents include HDAC inhibitors including 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 6,268,137, 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.

[0112] 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. Some non-limiting examples of known chemotherapeutic agents include 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 (LUCERTIS[®]), rituximab (RITUXAN[®]), tositumomab (BEXXAR[®]), trastuzumab (HERCEPTIN[®])), kinase inhibitors (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[®]), 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**, all of which are herein incorporated by reference in their entireties.

[0113] In another embodiment, the compounds of the present invention can be combined, with cytotoxic anti-cancer agents. Examples 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.

[0114] Other cytotoxic drugs suitable for use with the compounds of the invention 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.

[0115] Other cytotoxic anti-cancer agents suitable for use in combination with the compounds of the invention also include newly discovered cytotoxic principles such as oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, temozolomide (Quinn et al., *J. Clin. Oncol.*, **2003**, 21(4), 646-651), tositumomab (BEXXAR[®]), trabectedin (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).

[0116] In another embodiment, the compounds of the present invention can be combined with other signal transduction inhibitors. Examples of such agents include, by no way of limitation, 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.

[0117] In another embodiment, the compounds of the present invention can be combined with inhibitors of histone deacetylase. Examples of such agents include, by no way of limitation, suberoylanilide hydroxamic acid (SAHA), LAQ-824 (Ottmann et al., Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3024), LBH-589 (Becket 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 MGCD01 03 (US 6,897,220).

[0118] In another embodiment, the compounds of the present invention 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 of the present invention can be combined with other anti-cancer agents such as topoisomerase inhibitors, including but not limited to camptothecin.

[0119] 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.

[0120] 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 OF THE INVENTION

[0121] 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 of the invention is such that is effective to detectably inhibit or modulate a protein kinase, such as PI3K or mTOR activity. The compounds of the invention are useful in therapy as antineoplasia agents or to minimize deleterious effects of PI3K or mTOR signaling.

[0122] Compounds of the present invention 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 of the invention in an effective amount. Such diseases, conditions, or disorders include cancer, particularly metastatic cancer, atherosclerosis and lung fibrosis.

[0123] Compounds of the invention 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 lymphocytic 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, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer and Kaposi's sarcoma).

[0124] 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 hemangiomas, 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.

[0125] The compounds of the present invention are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy. The compounds of the present invention are also useful in the reduction of blood flow in a tumor in a subject. The compounds of the present invention are also useful in the reduction of metastasis of a tumor in a subject.

[0126] 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 of the present invention include the pharmaceutically acceptable derivatives thereof.

[0127] 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.

[0128] The treatment method that includes administering a compound or composition of the invention 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 of the invention 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 of the invention 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.

[0129] 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 of the invention, thereby causing inhibition of growth of the cell. 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.

[0130] 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 of the invention. 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.

[0131] 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.

[0132] 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.

[0133] 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, all of which are herein incorporated by reference in their entireties. 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, polysaccharides, 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

[0134] 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.

[0135] 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 of the invention, 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 of the invention.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] Column chromatography was conducted using a silica gel column. Silica gel (300 - 400 mesh) was purchased from Qingdao Ocean Chemical Factory. NMR spectra were recorded with a Bruker 400 MHz spectrometer at ambient temperature. NMR spectra were obtained as CDCl_3 , d_6 -DMSO, CD_3OD or d_6 -acetone solutions (reported in ppm), using TMS (0 ppm) or chloroform (7.25 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).

[0140] Low-resolution mass spectral (MS) data were generally determined on an Agilent 1200 Series LCMS (Zorbax SB-C18, 2.1 x 30 mm, 4 micorn, 10 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 210/254 nm and a low resonance electrospray mode (ESI).

[0141] Purities of compounds were assessed by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 210 nm and 254 nm. Column was normally operated at 40 °C.

[0142] The following abbreviations are used throughout the specification:

BBr_3 boron tribromide

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

BOC, Boc butyloxycarbonyl

BSA bovine serum albumin

CDCl_3 chloroform deuterated

CHCl_3 chloroform

CH_2Cl_2 , DCM methylene chloride

$\text{CH}_3\text{SO}_2\text{Cl}$, MsCl methanesulfonyl chloride

Cs_2CO_3 cesium carbonate

Cu copper

CuI cuprous iodide

DAST Diethylaminosulfur trifluoride

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	dimethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIEA, DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc, EA	ethyl acetate
EtOH	ethanol
Et ₂ O	diethyl ether
Et ₃ N, TEA	triethylamine
FBS	fetal bovine serum
Fe	iron
g	gram
h	hour
min	minute
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HBr	hydrobromic acid
HBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HCl	hydrochloric acid
H ₂	hydrogen
H ₂ O	water
H ₂ O ₂	hydrogen peroxide
HOAc	AcOH acetic acid

HOBt	1-hydroxybenzotriazole hydrate
K ₂ CO ₃	potassium carbonate
KOH	potassium hydroxide
KOAc	potassium acetate
LiHMDS	lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
MCPBA	<i>meta</i> -chloroperbenzoic acid
MeCN, CH ₃ CN	acetonitrile
MeI	methyl iodide
MeOH, CH ₃ OH	methanol
2-MeTHF	2-methyl tetrahydrofuran
MgSO ₄	magnesium sulfate
MsCl	methanesulfonyl chloride
mL, ml	milliliter
N ₂	nitrogen
NaBH ₄	sodium borohydride
NaBH ₃ CN	sodium cyanoborohydride
NaCl	sodium chloride
NaClO ₂	sodium chlorite
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaH ₂ PO ₄	sodium biphosphate
NaI	sodium iodide
NaO(<i>t</i> -Bu)	sodium <i>tert</i> -butoxide
NaOH	sodium hydroxide
Na ₂ SO ₄	sodium sulfate
Na ₂ SO ₃	sodium sulfite

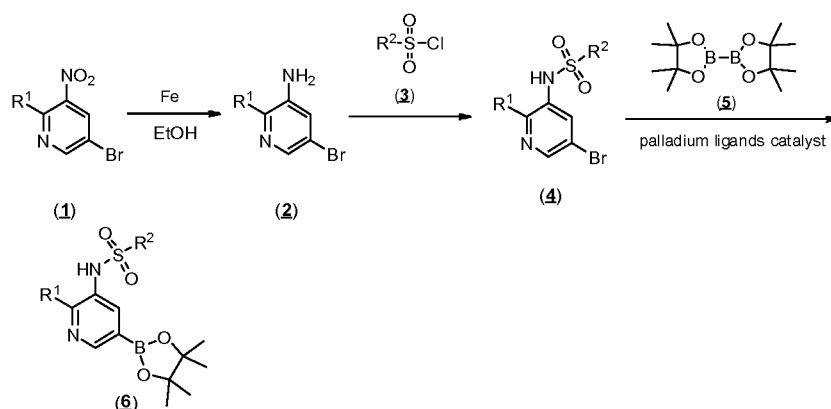
NBS	<i>N</i> -Bromosuccinimide
NH ₃	ammonia
NH ₄ Cl	ammonium chloride
NMP	<i>N</i> -methylpyrrolidinone
PBS	phosphate buffered saline
P(<i>t</i> -Bu) ₃	tri(tert-butyl)phosphine
Pd/C	palladium on carbon
Pd ₂ (dba) ₃	bis(dibenzylideneacetone) palladium
Pd(dppf)Cl ₂	1,1-bis(diphenylphosphino)ferrocene palladium dichloride
Pd(dppf)Cl ₂ ·CH ₂ Cl ₂	dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct
Pd(OAc) ₂	palladium acetate
Pd(OH) ₂	palladium hydroxide
Pd(PPh ₃) ₄	palladium tetrakis triphenylphosphine
Pd(PPh ₃) ₂ Cl ₂	Bis(triphenylphosphine)palladium(II) chloride
PE	petroleum ether (60-90 °C)
POCl ₃	phosphorous oxychloride
<i>i</i> -PrOH	isopropanol
PyBop	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
RT, rt, r.t.	room temperature
Rt	retention time
TBAB	tetrabutylammonium bromide
TBAHSO ₄	tetrabutylammonium hydrogen sulfate
TBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
TEAC	bis(<i>tetra</i> -ethylammonium)carbonate
THF	tetrahydrofuran

Zn(CN)₂ zinc cyanide

μL microliters

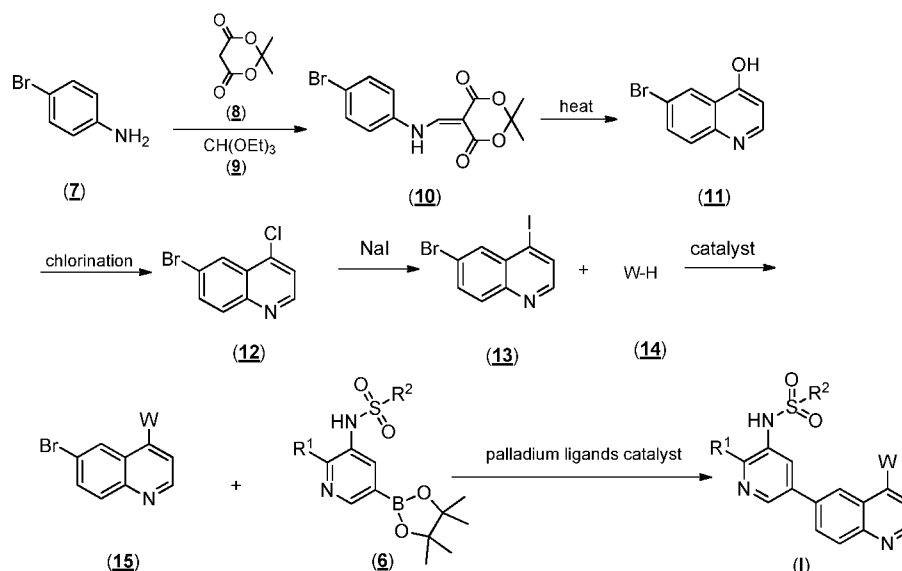
[0143] Outlined in **Schemes 1 to 5** are representative general procedures for preparing the compounds disclosed herein. Each R¹, R² and W represents appropriate groups as defined herein. Each W², X², R³, X⁴ represents appropriate groups. Unless otherwise indicated, W² is an optionally substituted C₅₋₁₂spirobicycyl; X² is an optionally substituted C₃₋₆heterocyclyl; R³, R⁴ is H or C₁₋₄alkyl.

Scheme 1



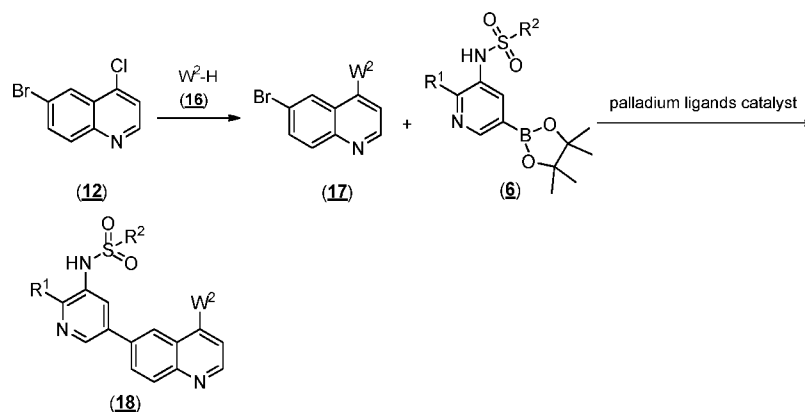
[0144] Boron ester derivative having Formula (6) can be prepared by a general method illustrated in **Scheme 1**. Substituted nitro-pyridine derivative (1) is reduced to amino-pyridine compound (2) under acidic condition using a reducing agent such as Fe powder. Then compound (2) is reacted with sulfonyl chloride (3) in the presence of a base to give brominated sulfonamide (4). The subsequent Suzuki coupling of brominated sulfonamide (4) with bis(pinacolato)diboron (5) in the presence of a suitable Pd catalyst affords boron ester derivative (6).

Scheme 2



[0145] Some compounds having Formula (I) can be prepared by a general method illustrated in **Scheme 2**. 4-Bromoanilines (7) is condensed with compounds (8) and (9) to furnish compound (10) in a solvent such as an alcoholic solvent. Compound (10) is then refluxed in a high boiling point solvent such as dichlorobenzene to give 6-bromo-4-hydroxyquinolin (11). The hydroxy group in (11) is converted to Cl using a chlorinating agent such as POCl_3 at an elevated temprature. Compound (12) is then converted to iodinated derivative (13) under acidic condition. Iodo-quinoline (13) is subsequently coupled with compound (14) in the presence of a suitable catalyst to give the intermediate (15). Final coupling of compound (15) with boron ester derivative (6) in the presence of an appropriate Pd catalyst affords a desired PI3K and/or mTOR inhibitor having formula (I) as disclosed herein.

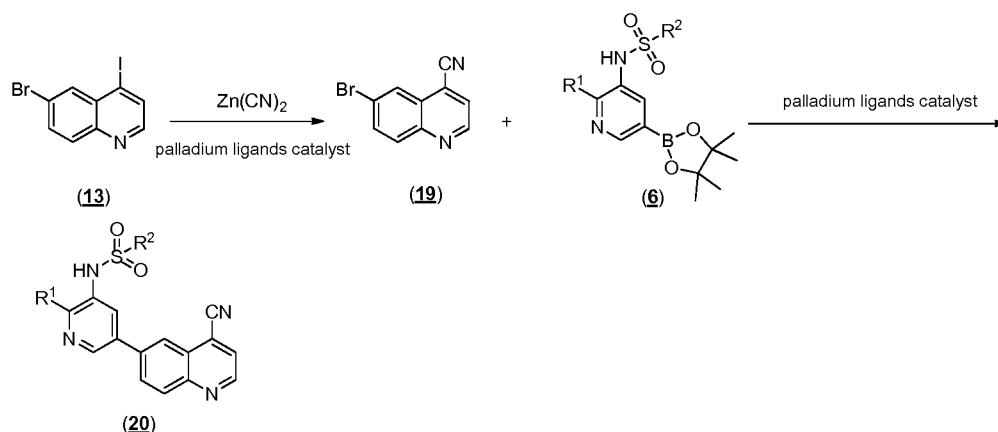
Scheme 3



[0146] The compounds disclosed herein may also be prepared by the method as described in **Scheme 3**. Thus, 6-bromo-4-chloroquinoline (12) is reacted with spirobicycle compound (16) to give compound (17). Then final coupling of compound (17) with boron ester derivative (6) in the

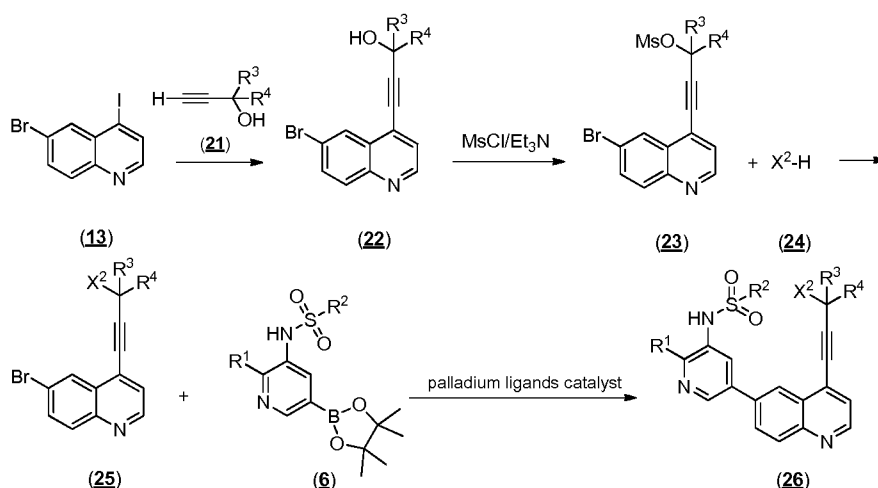
presence of an appropriate Pd catalyst affords a desired PI3K and/or mTOR inhibitor having formula (18) as disclosed herein.

Scheme 4



[0147] The compounds disclosed herein may also be prepared by the method as described in **Scheme 4**. Thus, 6-bromo-4-iodoquinoline (13) is coupled with $\text{Zn}(\text{CN})_2$ in the presence of a suitable Pd catalyst such as $\text{Pd}(\text{PPh}_3)_4$ to give 6-bromo-4-cyanoquinoline (19). Then final coupling of compound (19) with boron ester derivative (6) in the presence of an appropriate Pd catalyst affords a desired PI3K and/or mTOR inhibitor having formula (20) as disclosed herein.

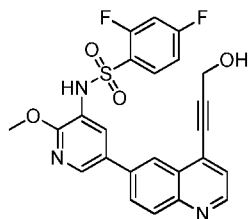
Scheme 5



[0148] The compounds disclosed herein may also be prepared by the method as described in **Scheme 5**. Thus, 6-bromo-4-iodoquinoline (13) is coupled with alkyne (21) in the presence of a suitable Pd catalyst affords alcohol compound (22). Alcohol compound (22) is then activated to methanesulfonate derivative (23) with the aid of a base such as Et_3N . Subsequent displacement of the methanesulfonate group in methanesulfonate derivative (23) with heterocycle (24) furnishes bromo-compound (25). Then final coupling of bromo-compound (25) with boron ester

derivative (**6**) in the presence of an appropriate Pd catalyst affords a desired PI3K and/or mTOR inhibitor having formula (**26**) as disclosed herein.

Example1 2,4-difluoro-N-(5-(4-(3-hydroxyprop-1-yn-1-yl)quinolin-6-yl)-2-methoxypyridin-3-yl) benzenesulfonamide



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

[0149] To a solution of sodium methanolate (0.52 g, 9.64 mmol) in MeOH (10 mL) was added 5-bromo-2-chloro-3-nitropyridine (0.57 g, 2.41 mmol) at 0°C. The reaction was stirred at 0°C for 1 h, then warmed up to rt and stirred further for 18 h. The reaction was quenched with H₂O (20 mL), adjusted to pH 7 with 3M HCl and then filtered. The separated organic phase was concentrated *in vacuo* to give the title compound as a light yellow solid (0.4 g, 71.4%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 233 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.93 (s, 3H), 8.08 (s, 1H), 8.89 (s, 1H).

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

[0150] To a suspension of 5-bromo-2-methoxy-3-nitropyridine (0.4 g, 1.72 mmol) in EtOH (5 mL) and H₂O (5 mL) was added iron powder (0.38 g, 6.87 mmol) and NH₄Cl (0.39 g, 7.21 mmol). The reaction refluxed for 1 h, then cooled down to rt and concentrated *in vacuo*. The residue was diluted with EtOAc (10 mL) and the resulted mixture was filtered through a pad of celite. The filtrate was extracted with EtOAc (10 mL x 3) and the combined organic phases were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound as a yellow solid (0.3 g, 86%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 203 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.92 (s, 3H), 4.86 (s, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H).

Step 3) N-(5-bromo-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0151] To a suspension of 5-bromo-2-methoxypyridin-3-amine (6.3 g, 31 mmol) in pyridine

(25 mL) was added 2,4-difluorobenzene-1-sulfonyl chloride (16.47 g, 77.5 mmol). The reaction was stirred at 23°C for 24 h. The solvent volume was then reduced to 50% under reduced pressure. The resulted solid was collected by filtration, and was washed with *i*-PrOH (5 mL x 2) followed by Et₂O (5 mL). A suspension of the above solid and NaOH (2.48 g, 62 mmol) in MeOH (25 mL) was stirred at 23°C for 1 h and then concentrated *in vacuo*. The residue was diluted with DCM (20 mL) and 2M HCl (20 mL), adjusted to pH 7 with 5% aq. NaHCO₃, and then extracted with DCM (20 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound as a pale yellow solid (8.2 g, 69.9%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 379 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.89 (s, 3H), 6.90-7.01 (m, 2H), 7.80-7.83 (d, *J* = 2.24 Hz, 1H), 7.86-7.93 (m, 2H).

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

[0152] To a suspension of N-(5-bromo-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (0.5 g, 1.31 mmol), bis(pinacolato)diboron (0.5 g, 1.97 mmol) and PdCl₂(dppf)·CH₂Cl₂ (80 mg, 0.1 mmol) in 1,4-dioxane (10 mL) was added KOAc (0.52 g, 5.24 mmol) under N₂ atmosphere. The reaction was heated to 90°C for 3 h and then cooled to rt. The mixture was diluted with 5% aq. NaHCO₃ (10 mL) and extracted with DCM (20 mL x 3). The combined organic phases were washed with brine (25 mL), dried over anhydrous Na₂SO₄ 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 white solid (0.31 g, 55.3%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 427 [M+H]⁺.

Step 5) 5-(((4-bromophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione

[0153] To a suspension of 4-bromobenzenamine (100 g, 0.58 mol) and triethyl orthoformate (103.5 mL, 0.62 mol) in EtOH (300 mL) was added Meldrum's acid (98.03 g, 0.68 mol). The reaction was stirred with mechanical agitation at 85°C for 4 h, then cooled down to 0°C. The solid was collected by filtration, and then washed with cooled anhydrous EtOH (300 mL) to give the title compound as a pale solid (176 g, 92%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 326 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.75 (s, 6H), 7.13 (m, 2H), 7.55 (m, 2H), 8.57 (d, *J* = 14.16 Hz, 1H), 11.20 (d, *J* = 13.44 Hz, 1H).

Step 6) 6-bromo-4-hydroxyquinolin

[0154] A mixture of 5-(((4-bromophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (50 g, 154 mmol) in 1,2-dichlorobenzene (500 mL) was stirred at 188°C for 3.5 h. The reaction was then cooled down to 0°C and stirred further for 3 h. The solid was collected by filtration, and was then washed with methyl tert-butyl ether (100 mL) to give the title compound as a brown solid (30.6 g, 87%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 224 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.32 (d, *J* = 7.32 Hz, 1H), 7.48 (d, *J* = 9.08 Hz, 1H), 7.77 (dd, *J* = 8.88 Hz, 2.32 Hz, 1H), 7.95 (d, *J* = 7.32 Hz, 1H), 8.34 (d, *J* = 2.28 Hz, 1H).

Step 7) 6-bromo-4-chloroquinoline

[0155] To a suspension of 6-bromo-4-hydroxyquinolin (14.55 g, 64.9 mmol) in toluene (20 mL) was added POCl₃ (6.05 mL, 64.9 mmol) slowly. The reaction was stirred at 115°C for 4 h, then cooled down to 0°C and diluted with DCM (400 mL). The mixture was washed with 4M NaOH (70 mL) followed by brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was recrystallized in *n*-heptane (150 mL) to give the title compound as a yellow solid (5.5 g, 32%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 242 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.50 (d, *J* = 4.72 Hz, 1H), 7.82 (dd, *J* = 8.96 Hz, 2.16 Hz, 1H), 7.98 (d, *J* = 8.92 Hz, 1H), 7.95 (d, *J* = 2.16 Hz, 1H), 8.34 (d, *J* = 4.68 Hz, 1H).

Step 8) 6-bromo-4-iodoquinoline

[0156] To a solution of 6-bromo-4-chloroquinoline (3 g, 12.4 mmol) in anhydrous THF (50 mL) was added 2M HCl in diethylether (7.4 mL, 14.8 mmol). The reaction was stirred at rt for 30 min and concentrated *in vacuo* to provide 6-bromo-4-chloro-quinoline hydrochloride as an off-white solid (3.46 g).

[0157] To a suspension of 6-bromo-4-chloro-quinoline hydrochloride (3.46 g) in propionitrile (100 mL) was added anhydrous sodium iodide (9.3 g, 62 mmol). The reaction was

refluxed for 96 h, then cooled down to rt. The mixture was treated with 10% aq. K_2CO_3 (50 mL), followed by 5% aq. Na_2SO_3 (20 mL), and then extracted with DCM (50 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the title compound as an off-white solid (3.4 g, 82.3%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 334 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78-7.83 (m, 1H), 7.89-7.93 (d, $J = 8.9$ Hz, 1H), 7.98-8.02 (m, 1H), 8.21 (s, 1H), 8.44-8.47 (d, $J = 4.5$ Hz, 1H).

Step 9) 6-bromo-4-(3-hydroxyprop-1-yn-1-yl)quinoline

[0158] To a suspension of 6-bromo-4-iodoquinoline (0.5 g, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (53 mg, 75 μ mol) and CuI (14.3 mg, 75 μ mol) in DMF (2 mL) was added prop-2-yn-1-ol (84 mg, 1.5 mmol) and Et_3N (0.63 g, 6.2 mmol). The reaction was stirred at rt for 1 h, then diluted with 5% aq. $NaHCO_3$ (10 mL) and extracted with DCM (20 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized in EtOAc (5 mL) to give the title compound as a light yellow solid (0.3 g, 76.9%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 262 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.49 (s, 1H), 4.68 (s, 2H), 7.46-7.49 (d, $J = 4.48$ Hz, 1H), 7.78-7.83 (m, 1H), 7.96-8.00 (d, $J = 8.96$ Hz, 1H), 8.35-8.38 (d, $J = 2.16$ Hz, 1H), 8.84-8.88 (d, $J = 4.48$ Hz, 1H).

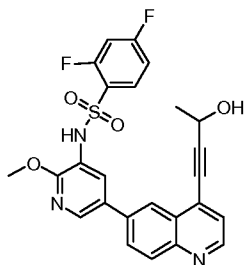
Step 10) 2,4-difluoro-N-(5-(4-(3-hydroxyprop-1-ynyl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0159] To a suspension of 6-bromo-4-(3-hydroxyprop-1-yn-1-yl)quinoline (0.54 g, 2.06 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.56 g, 1.31 mmol) and $Pd(PPh_3)_2Cl_2$ (175 mg, 0.25 mmol) in DMF (8 mL) and H_2O (1 mL) was added Na_2CO_3 (0.6 g, 7.5 mmol). The reaction was microwaved at 120 °C for 20 min and then cooled down to rt. The mixture was diluted with 5% aq. $NaHCO_3$ (10 mL) and extracted with DCM (20 mL x 3). The combined organic phases were washed with brine (20 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) = 50/1) to give the title compound as a light yellow solid (48 mg, 8.6%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 482 $[M+H]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 2.22 (s, 1H), 3.98 (s, 3H), 4.69 (s, 2H), 6.93-6.97 (m, 2H), 7.52 (d, $J = 15.6$ Hz, 1H), 7.89-7.92 (m, 2H), 8.17-8.19 (m, 2H), 8.25 (d, $J = 22.8$ Hz, 1H), 8.37 (d, $J = 20.4$ Hz, 1H), 8.89 (d, $J = 4.4$ Hz, 1H).

Example 2 2,4-difluoro-N-(5-(4-(3-hydroxybut-1-yn-1-yl)quinolin-6-yl)-2-methoxypyridin-3-yl) benzenesulfonamide



Step 1) 6-bromo-4-(3-hydroxybut-1-yn-1-yl)quinoline

[0160] The title compound was prepared according to the procedure as described in **Example 1 Step 9** by using 6-bromo-4-iodoquinoline (0.5 g, 1.5 mmol), but-3-yn-2-ol (105 mg, 1.5 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (53 mg, 75 μmol), CuI (14.3 g, 75 μmol) and Et_3N (0.63 g, 6.2 mmol) in DMF (2 mL). The crude product was recrystallized in EtOAc (5 mL) to give the title compound as a light yellow solid (0.35 g, 85.4%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 276 $[M+H]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.67 (d, $J = 7.6$ Hz, 3H), 2.29 (d, $J = 7.6$ Hz, 1H), 4.92-4.94 (m, 1H), 7.48 (d, $J = 4.4$ Hz, 1H), 7.79-7.82 (m, 1H), 7.97 (d, $J = 9.6$ Hz, 1H), 8.36 (d, $J = 2.4$ Hz, 1H), 8.86 (d, $J = 4.4$ Hz, 1H).

Step 2) 2,4-difluoro-N-(5-(4-(3-hydroxybut-1-yn-1-yl)quinolin-6-yl)-2-methoxypyridin-3-yl) benzenesulfonamide

[0161] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-hydroxybut-1-yn-1-yl)quinoline (0.57 g, 2.06 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)

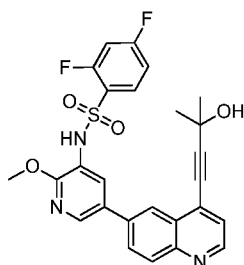
benzenesulfonamide (0.56 g, 1.31 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (175 mg, 0.25 mmol) and Na_2CO_3 (0.6 g, 5.66 mmol) in a mixture of DMF (8 mL) and H_2O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (85 mg, 13.4%). The title compound was characterized by LC-MS and ^1H

NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 496 $[M+H]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.70 (m, 3H), 3.49 (s, 1H), 3.98 (s, 3H), 4.95 (s, 1H), 6.93-6.97 (m, 2H), 7.50 (d, $J = 4.4$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 2H), 8.17 (d, $J = 8.0$ Hz, 2H), 8.26 (s, 1H), 8.36 (s, 1H), 8.87 (d, $J = 4.0$ Hz, 1H).

Example 3 2,4-difluoro-N-(5-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinolin-6-yl)-2-methoxy pyridin-3-yl)benzenesulfonamide



Step 1) 6-bromo-4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinoline

[0162] The title compound was prepared according to the procedure as described in **Example 1 Step 9** by using 6-bromo-4-iodoquinoline (0.5 g, 1.5 mmol), 2-methylbut-3-yn-2-ol (126 mg, 1.5 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (53 mg, 75 μmol), CuI (14.3 mg, 75 μmol) and Et_3N (0.63 g, 6.2 mmol) in DMF (2 mL). The crude product was recrystallized in EtOAc (5 mL) to give the title compound as a light yellow solid (0.36 g, 82.7%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 290 $[M+H]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.74 (s, 6H), 2.19 (s, 1H), 7.47 (d, $J = 4.4$ Hz, 1H), 7.79-7.82 (m, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 8.34 (d, $J = 2.4$ Hz, 1H), 8.86 (d, $J = 4.4$ Hz, 1H).

Step 2) 2,4-difluoro-N-(5-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinolin-6-yl)-2-methoxy pyridin-3-yl)benzenesulfonamide

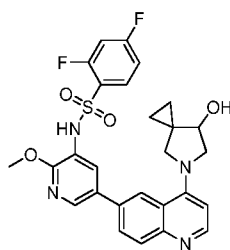
[0163] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinoline (0.6 g, 2.06 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.56 g, 1.31 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (175 mg, 0.25 mmol) and Na_2CO_3 (0.6 g, 5.66 mmol) in DMF (8 mL) and H_2O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (46 mg, 6.9%). The title compound was characterized by LC-MS and ^1H NMR as

shown below:

LC-MS (ESI, pos. ion) m/z : 510 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.76 (s, 6H), 2.44 (s, 1H), 3.97 (s, 3H), 6.92-6.97 (m, 2H), 7.49 (d, $J = 4.4$ Hz, 1H), 7.89-7.93 (m, 2H), 8.16 (s, 1H), 8.16-8.20 (m, 1H), 8.26 (d, $J = 2.4$ Hz, 1H), 8.37 (d, $J = 2.0$ Hz, 1H), 8.87 (d, $J = 4.4$ Hz, 1H).

Example 4 2,4-difluoro-N-(5-(4-(7-hydroxy-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 5-(6-bromoquinolin-4-yl)-5-azaspiro[2.4]heptan-7-ol

[0164] To a suspension of 6-bromo-4-chloroquinoline (0.29 g, 1.2 mmol) in DMF (2 mL) was added 5-azaspiro[2.4]heptan-7-ol (0.34 g, 3 mmol) under N_2 atmosphere. The reaction was stirred at $90^\circ C$ for 3 h, then cooled to rt. The mixture was diluted with $CHCl_3$ (5 mL) and washed with H_2O (5 mL). The resulted solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the title compound as a pale yellow solid (0.33 g, 86.8%). The title compound was characterized by LC-MS as shown below:

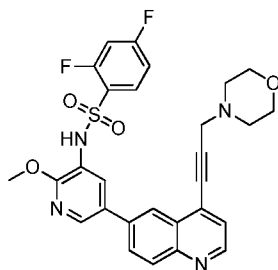
LC-MS (ESI, pos. ion) m/z : 319 $[M+H]^+$.

Step 2) 2,4-difluoro-N-(5-(4-(7-hydroxy-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0165] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 5-(6-bromoquinolin-4-yl)-5-azaspiro[2.4]heptan-7-ol (0.66 g, 2.06 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.56 g, 1.31 mmol), $Pd(PPh_3)_2Cl_2$ (175 mg, 0.25 mmol) and Na_2CO_3 (0.6 g, 5.66 mmol) in DMF (8 mL) and H_2O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (90 mg, 12.8%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z : 538 $[M+H]^+$.

Example 5 2,4-difluoro-N-(2-methoxy-5-(4-(3-morpholinoprop-1-yn-1-yl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

pyridin-3-yl)benzenesulfonamide**Step 1) 3-(6-bromoquinolin-4-yl)prop-2-yn-1-yl methanesulfonate**

[0166] To a mixture of 6-bromo-4-(3-hydroxyprop-1-yn-1-yl)quinoline (1.66 g, 6.33 mmol) in DCM (40 mL) was added Et₃N (1.28 g, 12.65 mmol) and MsCl (1.09 g, 9.5 mmol) at -10°C under N₂ atmosphere. The reaction was stirred at -10°C for 1 h, then quenched with saturated aq. NaHCO₃ (8 mL) and allowed to warm to rt. The separated organic phase dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to afford the title compound. The compound was used in next step without further purification. The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 340 [M+H]⁺.

Step 2) 4-(3-(6-bromoquinolin-4-yl)prop-2-yn-1-yl)morpholine

[0167] To a suspension of 3-(6-bromoquinolin-4-yl)prop-2-yn-1-yl methanesulfonate in MeCN (10 mL) was added morpholine (1.1 g, 1.1 mL, 12.6 mmol). The reaction was stirred at rt for 12 h, then quenched with H₂O (8 mL) and extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na₂SO₄ 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 (0.91 g, 43%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 331 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.72 (t, *J* = 4.6 Hz, 4H), 3.71 (s, 2H), 3.81 (t, *J* = 4.6 Hz, 4H), 7.50 (d, *J* = 4.4 Hz, 1H), 7.80 (dd, *J* = 9.0 Hz, 2.2 Hz, 1H), 8.40 (d, *J* = 9.0 Hz, 1H), 8.39 (d, *J* = 2.2 Hz, 1H), 8.85 (d, *J* = 4.5 Hz, 1H).

Step 3) 2,4-difluoro-N-(2-methoxy-5-(4-(3-morpholinoprop-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide

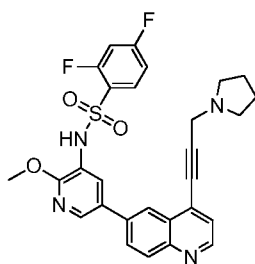
[0168] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 4-(3-(6-bromoquinolin-4-yl)prop-2-yn-1-yl)morpholine (0.23 g, 0.7

mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.2 g, 0.47 mmol), Pd(PPh₃)₂Cl₂ (66 mg, 94 μmol) and Na₂CO₃ (0.3 g, 2.82 mmol) in DMF (4 mL) and H₂O (0.5 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (50 mg, 19.4%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 551 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.75 (t, *J* = 4.56 Hz, 4H), 3.71 (s, 2H), 3.81 (t, *J* = 4.56 Hz, 4H), 3.95 (s, 3H), 6.90 - 6.99 (m, 2H), 7.52 (d, *J* = 4.44 Hz, 1H), 7.84 - 7.92 (m, 2H), 8.12 (d, *J* = 2.24 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 2.2 Hz, 1H), 8.37 (d, *J* = 1.84 Hz, 1H), 8.86 (d, *J* = 4.48 Hz, 1H).

Example 6 2,4-difluoro-N-(2-methoxy-5-(4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide



Step 1) 6-bromo-4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)quinoline

[0169] The title compound was prepared according to the procedure as described in **Example 5 Step 2** by using 3-(6-bromoquinolin-4-yl)prop-2-yn-1-yl methanesulfonate (0.91 g, 2.67 mmol) and pyrrolidine (0.88 mL, 10.7 mmol) in MeCN (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a yellow solid (0.21 g, 25%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 315 [M+H]⁺.

Step 2) 2,4-difluoro-N-(2-methoxy-5-(4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide

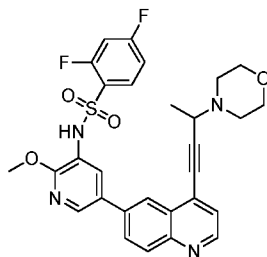
[0170] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)quinoline (0.21 g, 0.67 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-

-3-yl)benzenesulfonamide (0.19 g, 0.45 mmol), Pd(PPh₃)₂Cl₂ (63 mg, 90 μmol) and Na₂CO₃ (0.28 g, 2.67 mmol) in DMF (4 mL) and H₂O (0.5 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (30 mg, 12.6%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 535 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.88 (m, 4H), 2.79 (m, 4H), 3.96 (s, 3H), 5.29 (s, 2H), 6.90-6.99 (m, 2H), 7.52 (d, *J* = 4.48 Hz, 1H), 7.84-7.92 (m, 2H), 8.12 (d, *J* = 2.24 Hz, 1H), 8.18 (d, *J* = 8.76 Hz, 1H), 8.25 (d, *J* = 2.24 Hz, 1H), 8.37 (d, *J* = 1.96 Hz, 1H), 8.86 (d, *J* = 4.44 Hz, 1H).

Example 7 2,4-difluoro-N-(2-methoxy-5-(4-(3-morpholinobut-1-yn-1-yl)quinolin-6-yl)pyridin -3-yl)benzenesulfonamide



Step 1) 4-(6-bromoquinolin-4-yl)but-3-yn-2-yl methanesulfonate

[0171] The title compound was prepared according to the procedure as described in **Example 5 Step 1** by using 6-bromo-4-(3-hydroxybut-1-yn-1-yl)quinoline (0.5 g, 1.81 mmol), Et₃N (0.51 mL, 3.62 mmol) and MsCl (0.21 mL, 2.72 mmol) in DCM (6 mL). The title compound was obtained and used in the next step without further purification. The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 354 [M+H]⁺.

Step 2) 4-(4-(6-bromoquinolin-4-yl)but-3-yn-2-yl)morpholine

[0172] The title compound was prepared according to the procedure as described in **Example 5 Step 2** by using 4-(6-bromoquinolin-4-yl)but-3-yn-2-yl methanesulfonate (0.64 g, 1.81 mmol) and morpholine (0.31 mL, 3.61 mmol) in MeCN (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as yellow sticky liquid (0.38 g, 61%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 345 [M+H]⁺;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.54 (d, $J = 7.04$, 3H), 2.62-2.68 (m, 2H), 2.78-2.86 (m, 2H), 3.77-3.84 (m, 4H), 3.84-3.99 (m, 1H), 7.48 (d, $J = 4.48$ Hz, 1H), 7.78 (dd, $J = 8.92$ Hz, 2.2 Hz, 1H), 7.85 (d, $J = 8.96$ Hz, 1H), 8.38 (d, $J = 2.2$ Hz, 1H), 8.84 (d, $J = 4.44$ Hz, 1H).

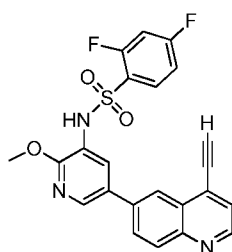
Step 3) 2,4-difluoro-N-(2-methoxy-5-(4-(3-morpholinobut-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide

[0173] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 4-(4-(6-bromoquinolin-4-yl)but-3-yn-2-yl)morpholine (0.23 g, 0.67 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.19 g, 0.45 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (63 mg, 90 μmol) and Na_2CO_3 (0.28 g, 2.67 mmol) in DMF (4 mL) and H_2O (0.5 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (67 mg, 26%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 565 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.56 (d, $J = 7.08$ Hz, 3H), 2.66-2.74 (m, 2H), 2.83-2.92 (m, 2H), 3.78-3.85 (m, 4H), 3.85-3.94 (m, 1H), 3.94 (s, 3H), 6.90-6.98 (m, 2H), 7.52 (d, $J = 4.48$ Hz, 1H), 7.83-7.92 (m, 2H), 8.13 (d, $J = 2.24$ Hz, 1H), 8.17 (d, $J = 8.72$ Hz, 1H), 8.27 (d, $J = 2.24$ Hz, 1H), 8.41 (d, $J = 1.96$ Hz, 1H), 8.87 (d, $J = 4.48$ Hz, 1H).

Example 8 N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzene sulfonamide



Step 1) 6-bromo-4-((trimethylsilyl)ethynyl)quinoline

[0174] To a suspension of 6-bromo-4-iodoquinoline (0.51 g, 1.53 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (56 mg, 80 μmol) and CuI (18.3 mg, 96 μmol) in DMF (4 mL) was added trimethylsilylacetylene (0.22 mL, 1.56 mmol) and Et_3N (1 mL, 7.17 mmol) under N_2 atmosphere. The reaction was stirred at rt for 20 min, then diluted with 5% aq. NaHCO_3 (30 mL) and extracted with CHCl_3 (50 mL). The organic phase was washed with H_2O (50 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 yellow powder (0.43 g, 94.2%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 304 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 0.35 (s, 9H), 7.71(d, *J* = 4.4 Hz, 1H), 7.98 (dd, *J* = 2.2 Hz, 8.9 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 8.29 (d, *J* = 2.1 Hz, 1H), 8.94 (d, *J* = 4.4 Hz, 1H).

Step 2) 2,4-difluoro-N-(2-methoxy-5-(4-((trimethylsilyl)ethynyl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide

[0175] To a suspension of 6-bromo-4-((trimethylsilyl)ethynyl)quinoline (0.43 g, 1.41 mmol),

2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzene sulfonamide (0.56 g, 1.35 mmol), Pd(PPh₃)₂Cl₂ (0.13 g, 0.19 mmol) in 1,4-dioxane (12 mL) and H₂O (2 mL) was added Na₂CO₃ (0.66 g, 6.23 mmol) under N₂ atmosphere. The reaction was stirred at 90°C for 30 min and then cooled to rt. The mixture was diluted with 5% aq. NaHCO₃ (10 mL) and extracted with DCM (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/3) to give the title compound as yellow oil (0.27 g, 28%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 524 [M+H]⁺.

Step 3) N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

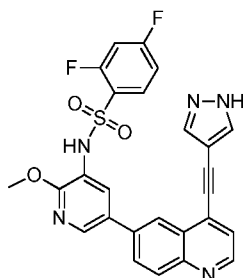
[0176] To a solution of 2,4-difluoro-N-(2-methoxy-5-(4-((trimethylsilyl)ethynyl) quinolin-6-yl) pyridin-3-yl)benzenesulfonamide (3.86 g, 7.73 mmol) in MeOH (150 mL) and THF (60 mL) was added KOH (0.83 g, 14.82 mmol) in MeOH (4 mL). The reaction was stirred at rt for 2 h and concentrated *in vacuo*. The residue was diluted with H₂O (100 mL) and MeOH (5 mL), then extracted with DCM (100 mL x 3). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/3) to give the title compound as a pink crystal solid (1.44 g, 43.3%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 452 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 3.70 (s, 3H), 5.13 (s, 1H), 7.23 (td, *J* = 2.1 Hz, 8.2 Hz, 1H), 7.58 (td, *J* = 2.5 Hz, 9.5 Hz, 1H), 7.75 (d, *J* = 4.4 Hz, 1H), 7.80 (td, *J* = 6.4 Hz, 8.5 Hz, 1H),

7.97 (d, $J = 2.3$ Hz, 1H), 8.13 (dd, $J = 2.0$ Hz, 8.8 Hz, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 8.28 (d, $J = 1.8$ Hz, 1H), 8.46 (d, $J = 1.8$ Hz, 1H), 8.94 (d, $J = 4.4$ Hz, 1H), 10.45 (s, 1H).

Example 9 N-(5-(4-((1H-pyrazol-4-yl)ethynyl)quinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide



Step 1) 4-((trimethylsilyl)ethynyl)-1H-pyrazole

[0177] To a suspension of 4-iodo-1H-pyrazole (2.91 g, 15 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.1 g, 1.57 mmol), CuI (0.29 g, 1.52 mmol) in EtOH (25 mL) and Et_3N (6 mL) was added trimethylsilylacetylene (2.5 mL, 17.58 mmol). The reaction was stirred at 70°C for 4 h, then cooled down to rt and concentrated *in vacuo*. The residue was diluted with EtOAc (30 mL) and then filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 3/2) to give the title compound as an orange solid (1.97 g, 79.9%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 165 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 0.19 (s, 9H), 7.65 (s, 1H), 8.06 (s, 1H), 13.11 (s, 1H).

Step 2) 4-ethynyl-1H-pyrazole

[0178] To a solution of 4-((trimethylsilyl)ethynyl)-1H-pyrazole (1.97 g, 11.99 mmol) in MeOH (40 mL) was added KOH (1.36 g, 24.29 mmol) in MeOH (6 mL). The reaction was stirred at rt for 5 h 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 white powder (0.48 g, 43.5%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 93 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.93 (s, 1H), 7.65 (s, 1H), 8.04 (s, 1H), 13.08 (s, 1H).

Step 3) 4-((1H-pyrazol-4-yl)ethynyl)-6-bromoquinoline

[0179] To a suspension of 6-bromo-4-iodoquinoline (1 g, 3 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.11 g, 0.16 mmol), CuI (36 mg, 0.19 mmol) and 4-ethynyl-1H-pyrazole (0.28 g, 3 mmol) in DMF (8

mL) was added Et₃N (2 mL, 14.34 mmol) under N₂ atmosphere. The reaction was stirred at 90°C for 1 h, then cooled down to rt. The mixture was diluted with 5% aq. Na₂CO₃ (20 mL) and extracted with DCM (40 mL). The organic phase was washed with H₂O (40 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to afford the title compound as white powder (0.53 g, 59.7%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 298 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.71 (d, *J* = 4.5 Hz, 1H), 7.96 (m, 1H), 7.99 (d, *J* = 2.16 Hz, 1H), 8.03 (d, *J* = 8.9 Hz, 1H), 8.41 (d, *J* = 1.9 Hz, 1H), 8.94 (d, *J* = 4.5 Hz, 1H).

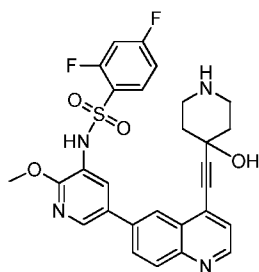
Step 4) N-(5-(4-((1H-pyrazol-4-yl)ethynyl)quinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0180] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 4-((1H-pyrazol-4-yl)ethynyl)-6-bromoquinoline (0.38 g, 1.28 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.54 g, 1.27 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.2 g, 0.24 mmol) and Na₂CO₃ (0.67 g, 6.32 mmol) in a mixture of DMF (8 mL) and H₂O (1 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as pale yellow powder (51 mg, 7.7%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 518 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 3.71 (s, 3H), 5.13 (s, 1H), 7.20 (td, *J* = 1.7 Hz, 8.4 Hz, 1H), 7.55 (td, *J* = 2.4 Hz, 9.8 Hz, 1H), 7.68 (d, *J* = 4.5 Hz, 1H), 7.77 (td, *J* = 6.5 Hz, 8.8 Hz, 1H), 7.98 (s, 1H), 8.10 (dd, *J* = 2.3 Hz, 7.6 Hz, 1H), 8.14 (d, *J* = 1.8 Hz, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 8.37 (s, 1H), 8.42 (s, 1H), 8.52 (d, *J* = 2.1 Hz, 1H), 8.91 (d, *J* = 4.4 Hz, 1H), 13.41 (s, 1H).

Example 10 2,4-difluoro-N-(5-(4-((4-hydroxypiperidin-4-yl)ethynyl)quinolin-6-yl)-2-methoxy pyridin-3-yl)benzenesulfonamide



Step 1) 1-(*tert*-butoxycarbonyl)-4-((trimethylsilyl)ethynyl)piperidin-4-ol

[0181] To a solution of trimethylsilylacetylene (8.5 mL, 46.07 mmol) in anhydrous THF (40 mL) was added *n*-BuLi (9.8 mL, 24.5 mmol) slowly at -40°C under N₂ atmosphere. The reaction was stirred at -40°C for 1 h and then cooled to -78°C followed by the addition of a solution of 1-(*tert*-butoxycarbonyl)piperidin-4-one (4.03 g, 20.23 mmol) in anhydrous THF (10 mL) via cannula. The reaction was stirred at -78°C for 1 h, then warmed to rt and continued to stir for 12 h. The reaction was quenched with saturated aq. NH₄Cl (15 mL), then poured into H₂O (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a silical gel column chromatography (PE/EtOAc (v/v) = 10/1) to give the title compound as a pale yellow crystal solid (6.08 g, 94%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 298 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.16 (s, 9H), 1.45 (s, 9H), 1.84 (td, *J* = 1.7 Hz, 2H), 2.03 (s, 2H), 2.43 (s, 1H), 3.20 (td, 2H), 3.77 (s, 2H).

Step 2) 1-(*tert*-butoxycarbonyl)-4-ethynylpiperidin-4-ol

[0182] To the solution of 1-(*tert*-butoxycarbonyl)-4-((trimethylsilyl)ethynyl)piperidin-4-ol (3.06 g, 10.29 mmol) in MeOH (40 mL) was added KOH (1.38 g, 24.64 mmol) in MeOH (4 mL). The reaction was stirred at rt for 6 h, then diluted with H₂O (40 mL) and extracted with EtOAc (50 mL x 4). The combined organic phases were dried over anhydrous Na₂SO₄ and concentration *in vacuo* to give the title compound as pale yellow powder (1.91 g, 75.9%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 226 [M+H]⁺.

Step 3) 4-(((6-bromoquinolin-4-yl)ethynyl)-1-(*tert*-butoxycarbonyl)piperidin-4-ol

[0183] The title compound was prepared according to the procedure as described in **Example 1 Step 9** by using 1-(*tert*-butoxycarbonyl)-4-ethynylpiperidin-4-ol (0.7 g, 3.11 mmol), 6-bromo-4-iodo quinoline (1 g, 3.11 mmol), Pd(PPh₃)₂Cl₂ (0.12 g, 0.17 mmol), CuI (46 mg, 0.24 mmol) and Et₃N (2 mL, 14.34 mmol) in DMF (8 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 7/3) to give the title compound as pale yellow powder (1.24 g, 92.74%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 431 [M+H]⁺.

Step 4) N-(5-(4-((1-(tert-butoxycarbonyl)-4-hydroxypiperidin-4-yl)ethynyl)quinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0184] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 4-((6-bromoquinolin-4-yl)ethynyl)-1-(tert-butoxycarbonyl)-Piperidin-4-ol (0.55 g, 1.28 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl) benzenesulfonamide (0.54 g, 1.27 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.2 g, 0.24 mmol) and Na₂CO₃ (0.67 g, 6.32 mmol) in a mixture of DMF (8 mL) and H₂O (1 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/3) to give the title compound as yellow oil (0.37 g, 44.4%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 651 [M+H]⁺.

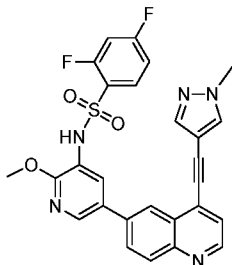
Step 5) 2,4-difluoro-N-(5-(4-((4-hydroxypiperidin-4-yl)ethynyl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0185] To a solution of N-(5-(4-((1-(tert-butoxycarbonyl)-4-hydroxypiperidin-4-yl)ethynyl)-quinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (0.37 g, 0.57 mmol) in anhydrous DCM (20 mL) was added a saturated solution of HCl in EtOAc (6 mL, 15 mmol) at rt. The reaction was stirred at rt 16 h, and then filtered. The solid was diluted with 5% aq. NaHCO₃ (100 mL) and extracted with a mixture of DCM and MeOH ((50 mL:1 mL) x 3). The organic phase was dried over anhydrous Na₂SO₄ and 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 yellow powder (90 mg, 28.73%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 551 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 2.14 (2H), 2.24 (2H), 3.26 (2H), 3.51 (2H), 3.73 (s, 3H), 6.42 (s, 1H), 7.18 (td, *J* = 2.2 Hz, 8.4 Hz, 1H), 7.48 (td, *J* = 1.7 Hz, 9.4 Hz, 1H), 7.69 (d, *J* = 4.4 Hz, 1H), 7.81 (td, *J* = 6.6 Hz, 8.6 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 8.09 (dd, *J* = 6.9 Hz, 1.9 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.34 (d, *J* = 1.8 Hz, 2H), 8.91 (d, *J* = 4.4 Hz, 1H).

Example 11 2,4-difluoro-N-(2-methoxy-5-(4-((1-methyl-1H-pyrazol-4-yl)ethynyl)quinolin-6-yl) pyridin-3-yl)benzenesulfonamide



Step 1) 4-iodo-1-methyl-1H-pyrazole

[0186] To a solution of 4-iodo-1H-pyrazole (3.88 g, 20 mmol) in DMF (50 mL) was added NaH (1.66 g, 55.33 mmol, 80% dispersion in mineral oil) at 0°C under N₂ atmosphere. The reaction was stirred at 0°C for 10 min followed by the addition of CH₃I (2.5 mL, 38.76 mmol) slowly. The mixture was stirred at rt for 22 h, then quenched with H₂O (100 mL) and extracted with EtOAc (200 mL). The organic phase was dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound as a pale yellow solid (3.99 g, 95.9%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 209 [M+H]⁺.

Step 2) 1-methyl-4-((trimethylsilyl)ethynyl)-1H-pyrazole

[0187] The title compound was prepared according to the procedure as described in **Example 9 Step 1** by using 4-iodo-1-methyl-1H-pyrazole (3.99 g, 19.18 mmol), trimethylsilylacetylene (3 mL, 21.26 mmol), Pd(PPh₃)₂Cl₂ (1.33 g, 1.9 mmol), CuI (0.36 g, 1.89 mmol) and Et₃N (8 mL) in EtOH (40 mL). The residue was purified via a silica gel column chromatography (PE/EtOAc (v/v) = 10/1) to give the crude product which was used in next step without further purification. The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 179 [M+H]⁺.

Step 3) 4-ethynyl-1-methyl-1H-pyrazole

[0188] The title compound was prepared according to the procedure as described in **Example 8 Step 3** by using 1-methyl-4-((trimethylsilyl)ethynyl)-1H-pyrazole and KOH (2.26 g, 40.36 mmol) in MeOH (36 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 10/3) to give the title compound as yellow oil (0.55 g, the total yield of the two steps was 27.1%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 107 [M+H]⁺.

Step 4) 6-bromo-4-((1-methyl-1H-pyrazol-4-yl)ethynyl)quinoline

[0189] To a solution of 4-ethynyl-1-methyl-1H-pyrazole (0.55 g, 5.19 mmol) in DMF (10 mL) was added 6-bromo-4-iodoquinoline (1.73 g, 5.19 mmol), Pd(PPh₃)₂Cl₂ (0.19 g, 0.27 mmol), CuI (0.12 g, 0.63 mmol) and Et₃N (4 mL) under N₂ atmosphere. The reaction was stirred at 90°C for 2 h and then heated to reflux for 1 h. The mixture was cooled down to rt, then diluted with 5% aq. Na₂CO₃ (50 mL) and extracted with a mixture of DCM and MeOH ((100 mL:1 mL) x 3). The combined organic phases were washed with H₂O (50 mL), dried over anhydrous Na₂SO₄ and concentration *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 powder (0.77 g, 47.5%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 312 [M+H]⁺.

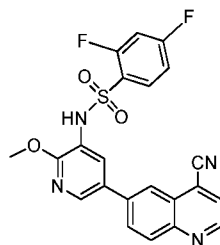
Step 5) 2,4-difluoro-N-(2-methoxy-5-(4-((1-methyl-1H-pyrazol-4-yl)ethynyl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide

[0190] To a suspension of 6-bromo-4-((1-methyl-1H-pyrazol-4-yl)ethynyl)quinoline (0.55 g, 1.76 mmol), 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl) benzenesulfonamide (0.55 g, 1.29 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.13 g, 0.16 mmol) in a mixture of DMF (8 mL) and H₂O (1 mL) was added Na₂CO₃ (0.67 g, 6.32 mmol) under N₂ atmosphere. The reaction was heated at 154°C for 1 h, then cooled down to rt. The mixture was diluted with 5% aq. NaHCO₃ (10 mL) and extracted with DCM (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/3) to give the title compound as pale yellow powder (226 mg, 33%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 532 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 3.72 (s, 3H), 3.91 (s, 3H), 7.21 (td, *J* = 2.0 Hz, 8.3 Hz, 1H), 7.6 (td, *J* = 2.4 Hz, 9.4 Hz, 1H), 7.68 (d, *J* = 4.5 Hz, 1H), 7.80 (td, *J* = 6.4 Hz, 8.6 Hz, 1H), 7.93 (s, 1H), 8.145 (m, 3H), 8.32 (s, 1H), 8.405 (d, *J* = 1.3 Hz, 1H), 8.53 (d, *J* = 2.3 Hz, 1H), 8.91 (d, *J* = 4.5 Hz, 1H), 10.45 (s, 1H).

Example 12 N-(5-(4-cyanoquinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzene sulfonamide



Step 1) 6-bromo-4-cyanoquinoline

[0191] To a mixture of 6-bromo-4-iodoquinoline (1.32 g, 4 mmol) in DMF (10 mL) was added $\text{Zn}(\text{CN})_2$ (235 mg, 2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (924 mg, 0.8 mmol) under N_2 atmosphere. The reaction was microwaved at 120°C for 30 min, then cooled down 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) = 5/1) to afford the title compound as a white solid (0.5 g, 54%). The title compound was characterized by LC-MS, ^1H NMR and ^{13}C NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 234.1 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.76 (d, $J = 4.36$ Hz, 1H), 7.94 (dd, $J = 8.96$ Hz, 2.12 Hz, 1H), 8.08 (d, $J = 8.96$ Hz, 1H), 8.36 (d, $J = 2.04$ Hz, 1H), 9.05 (d, $J = 4.36$ Hz, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 115.1, 117.7, 123.9, 125.5, 126.8, 127.2, 132.0, 134.9, 146.7, 149.7.

Step 2) N-(5-(4-cyanoquinolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

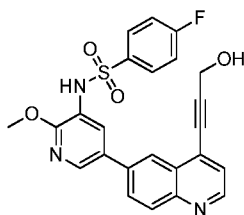
[0192] To a mixture of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-yl)benzenesulfonamide (0.64 g, 1.5 mmol) and 6-bromo-4-cyanoquinoline (348 mg, 1.5 mmol) in dioxane (15 mL) was added $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (184 mg, 0.23 mmol) and Na_2CO_3 (636 mg, 6 mmol) under N_2 atmosphere. The reaction was heated at 90°C for 2 h, then cooled down 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 afford the title compound as a white solid (245 mg, 36%). The title compound was characterized by LC-MS, ^1H NMR and ^{13}C NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 453 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 4.01 (s, 3H), 6.96 (td, $J = 8.48$ Hz, 2.36 Hz, 1H), 7.08 (td, $J = 8.62$ Hz, 1.64 Hz, 1H), 7.40 (s, 1H), 7.78 (d, $J = 4.32$ Hz, 1H), 8.01 (dd, $J = 8.80$ Hz, 1.64 Hz, 1H), 8.03-8.05 (m, 1H), 8.06 (d, $J = 2.20$ Hz, 1H), 8.15 (d, $J = 1.80$ Hz, 1H), 8.23 (d, $J = 2.20$ Hz, 1H), 8.29 (d, $J = 8.76$ Hz, 1H), 9.05 (d, $J = 4.32$ Hz, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 54.3, 105.9, 112.5, 115.5, 118.7, 121.0, 122.2, 125.4, 125.6, 126.1, 129.1, 130.3, 131.3, 132.8, 132.9, 138.2, 140.6, 147.5, 149.5, 154.3, 165.1, 167.7.

Example 13 4-fluoro-N-(5-(4-(3-hydroxyprop-1-ynyl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) N-(5-bromo-2-methoxypyridin-3-yl)-4-fluorobenzenesulfonamide

[0193] The title compound was prepared according to the procedure as described in **Example 1 Step 3** by using 5-bromo-2-methoxypyridin-3-amine (6.3 g, 31 mmol) and 4-fluorobenzene-1-sulfonyl chloride (15.08 g, 77.5 mmol) in pyridine (25 mL). The title compound was obtained as a pale yellow solid (9.12 g, 81.4%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 361 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 3.82 (s, 3H), 7.16 (m, 2H), 7.84 (m, 2H), 7.79 (d, $J = 2.0$ Hz, 2H).

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

[0194] The title compound was prepared according to the procedure as described in **Example 1 Step 4** by using N-(5-bromo-2-methoxypyridin-3-yl)-4-fluorobenzenesulfonamide (0.5 g, 1.38 mmol), bis(pinacolato)diboron (0.53 g, 2.07 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (80 mg, 0.1 mmol) and KOAc (0.54 g, 5.54 mmol) in 1,4-dioxane (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (0.29 g, 51.3%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z : 409 $[\text{M}+\text{H}]^+$.

Step 3) 4-fluoro-N-(5-(4-(3-hydroxyprop-1-ynyl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

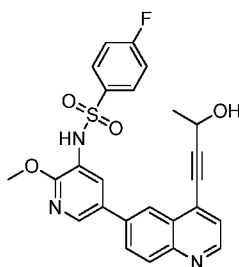
[0195] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-yl) benzenesulfonamide (0.53 g, 1.31 mmol), 6-bromo-4-(3-hydroxyprop-1-yn-

1-yl)quinoline (0.54 g, 2.06 mmol), Pd(PPh₃)₂Cl₂ (175 mg, 0.25 mmol) and Na₂CO₃ (0.6 g, 5.66 mmol) in a mixture of DMF (8 mL) and H₂O (1 mL). The crude product was purified via a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (59 mg, 9.8%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 464 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.20-2.24 (m, 1H), 3.89 (s, 3H), 4.69 (d, *J* = 6.4 Hz, 2H), 6.94 (s, 1H), 7.12-7.16 (m, 1H), 7.52 (d, *J* = 4.4 Hz, 1H), 7.82-7.86 (m, 2H), 7.92-7.95 (m, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.28 (d, *J* = 2.4 Hz, 1H), 8.41 (d, *J* = 2.0 Hz, 1H), 8.88 (d, *J* = 4.8 Hz, 1H).

Example 14 4-fluoro-N-(5-(4-(3-hydroxybut-1-yn-1-yl)quinolin-6-yl)-2-methoxypyridin-3-yl) benzenesulfonamide

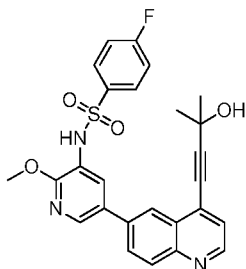


[0196] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-hydroxybut-1-yn-1-yl)quinoline (0.57 g, 2.06 mmol), 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-yl)benzenesulfonamide (0.53 g, 1.31 mmol), Pd(PPh₃)₂Cl₂ (175 mg, 0.25 mmol) and Na₂CO₃ (0.6 g, 5.66 mmol) in a mixture of DMF (8 mL) and H₂O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (11.3 mg, 1.8%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 478 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.69 (d, *J* = 7.6 Hz, 3H), 2.04 (s, 1H), 3.89 (s, 3H), 4.95 (s, 1H), 7.11-7.15 (m, 2H), 7.50 (d, *J* = 4.4 Hz, 2H), 7.83-7.86 (m, 2H), 7.93 (d, *J* = 8.8 Hz, 1H), 8.17-8.26 (m, 2H), 8.40 (s, 1H), 8.87 (d, *J* = 4.8 Hz, 1H).

Example 15 4-fluoro-N-(5-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

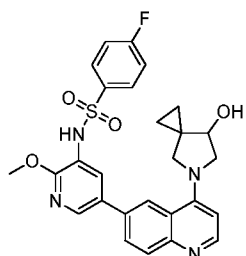


[0197] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinoline (0.6 g, 2.06 mmol), 4-fluoro- N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-yl)benzenesulfonamide (0.53 g, 1.31 mmol), Pd(PPh₃)₂Cl₂ (175 mg, 0.25 mmol) and Na₂CO₃ (0.6 g, 5.66 mmol) in DMF (8 mL) and H₂O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (12.8 mg, 2%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 492 [M+H]⁺;

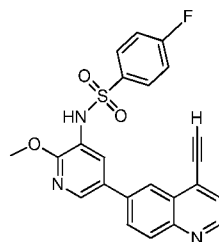
¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.75 (s, 6H), 3.89 (s, 3H), 6.98 (s, 1H), 7.11-7.15 (m, 1H), 7.49 (d, *J* = 4.4 Hz, 1H), 7.82-7.85 (m, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.26 (s, 2H), 8.40 (s, 1H), 8.87 (d, *J* = 4.4 Hz, 1H).

Example 16 4-fluoro-N-(5-(4-(7-hydroxy-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)-2-methoxy pyridin-3-yl)benzenesulfonamide



[0198] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 5-(6-bromoquinolin-4-yl)-5-azaspiro[2.4]heptan-7-ol (0.66 g, 2.06 mmol), 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-yl)benzenesulfonamide (0.53 g, 1.31 mmol), Pd(PPh₃)₂Cl₂ (175 mg, 0.25 mmol) and Na₂CO₃ (0.6 g, 5.66 mmol) in DMF (8 mL) and H₂O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (18 mg, 2.7%). The title compound was characterized by LC-MS as shown below:

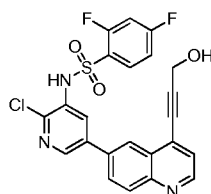
LC-MS (ESI, pos. ion) m/z: 520 [M+H]⁺.

Example 17 N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)-4-**fluorobenzenesulfonamide**

[0199] The title compound was prepared according to the procedure as described in **Example 8 Step 2** by using 6-bromo-4-((trimethylsilyl)ethynyl)quinoline (457 mg, 1.5 mmol), 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (735 mg, 1.8 mmol), PdCl₂(dppf)·CH₂Cl₂ (184 mg, 0.23 mmol) and Na₂CO₃ (795 mg, 7.5 mmol) in 1,4-dioxane (15 mL) and H₂O (3 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/2) to afford the title compound as white powder (23.5 mg, 4%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 434 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.74 (s, 1H), 3.90 (s, 3H), 7.02 (s, 1H), 7.15 (t, *J* = 8.44 Hz, 2H), 7.60 (d, *J* = 4.44 Hz, 1H), 7.86 (dd, *J* = 8.80 Hz, 5.00 Hz, 2H), 7.91 (dd, *J* = 8.72 Hz, 1.92 Hz, 1H), 8.14 (d, *J* = 2.12 Hz, 1H), 8.21 (d, *J* = 8.76 Hz, 1H), 8.25 (d, *J* = 2.16 Hz, 1H), 8.37 (d, *J* = 1.80 Hz, 1H), 8.90 (d, *J* = 4.44 Hz, 1H).

Example 18 N-(2-chloro-5-(4-(3-hydroxyprop-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)-2,4-**difluoro benzenesulfonamide****Step 1) N-(5-bromo-2-chloropyridin-3-yl)-2,4-difluorobenzenesulfonamide**

[0200] The title compound was prepared according to the procedure as described in **Example 1 Step 3** by using 5-bromo-2-chloropyridin-3-amine (6.43 g, 31 mmol) and 2,4-difluorobenzene-1-sulfonyl chloride (16.47 g, 77.5 mmol) in pyridine (25 mL). The title compound was obtained as a pale yellow solid (8.48 g, 71.3%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 383 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.26 (td, *J* = 2.56 Hz, 8.50 Hz, 1H), 7.57 (td, *J* = 2.48 Hz, 9.60 Hz, 1H), 7.82 (td, *J* = 6.24 Hz, 8.64 Hz, 1H), 8.03 (d, *J* = 7.28 Hz, 1H), 8.45 (d, *J* = 1.84 Hz, 1H).

Step 2) N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0201] The title compound was prepared according to the procedure as described in **Example 1 Step 4** by using N-(5-bromo-2-chloropyridin-3-yl)-2,4-difluorobenzenesulfonamide (0.5 g, 1.31 mmol), bis(pinacolato)diboron (0.5 g, 1.97 mmol), PdCl₂(dppf)·CH₂Cl₂ (80 mg, 0.1 mmol) and KOAc (0.52 g, 5.24 mmol) in 1,4-dioxane (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (0.35 g, 62.5%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 431 [M+H]⁺.

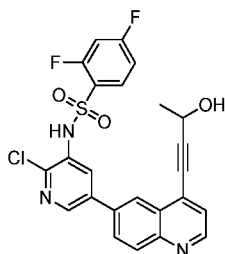
Step 3) N-(2-chloro-5-(4-(3-hydroxyprop-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0202] To a suspension of 6-bromo-4-(3-hydroxyprop-1-yn-1-yl)quinoline (0.37 g, 1.41 mmol), N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-2,4-difluorobenzene sulfonamide (568 mg, 1.32 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.2 g, 0.24 mmol) in 1,4-dioxane (12 mL) and H₂O (1 mL) was added Na₂CO₃ (0.6 g, 5.66 mmol) under N₂ atmosphere. The reaction was heated at 90°C for 1.5 h, then cooled down to rt, diluted with CHCl₃ (20 mL) and 5% aq. NaHCO₃ (10 mL). The separated organic phase was dried over anhydrous Na₂SO₄ 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 white powder (75 mg, 11.7%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 486 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 4.53 (s, 2H), 5.32 (s, 1H), 7.25 (td, *J* = 2.04 Hz, 8.20 Hz, 1H), 7.59 (t, *J* = 8.68 Hz, 1H), 7.69 (d, *J* = 4.44 Hz, 1H), 7.85 (td, *J* = 6.24 Hz, 8.48 Hz, 1H), 8.16 (d, *J* = 1.96 Hz, 8.76 Hz, 1H), 8.21 (d, *J* = 4.56 Hz, 1H), 8.22 (s, 1H), 8.46 (d, *J* = 1.84 Hz, 1H), 8.75 (s, 1H), 8.95 (d, *J* = 4.36 Hz, 1H).

Example 19 N-(2-chloro-5-(4-(3-hydroxybut-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)-2,4-difluoro benzenesulfonamide

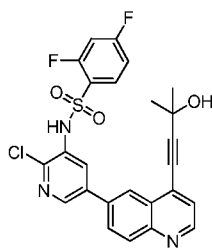


[0203] To a suspension of 6-bromo-4-(3-hydroxybut-1-yn-1-yl)quinoline (379 mg, 1.38 mmol), N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-2,4-difluorobenzene sulfonamide (568 mg, 1.32 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (0.2 g, 0.24 mmol) in 1,4-dioxane (12 mL) and H_2O (1 mL) was added Na_2CO_3 (0.6 g, 5.66 mmol) under N_2 atmosphere. The reaction was heated at 100°C for 1 h, then diluted with DCM (20 mL) and 5% aq. NaHCO_3 (10 mL). The separated organic phase was 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 pale yellow powder (88 mg, 13.4%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 500 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 1.53 (d, $J = 6.64$ Hz, 3H), 2.22 (q, $J = 6.56$ Hz, 1H), 5.76 (s, 1H), 7.25 (td, $J = 2.08$ Hz, 8.40 Hz, 1H), 7.58 (td, $J = 2.00$ Hz, 9.52 Hz, 1H), 7.67 (d, $J = 4.44$ Hz, 1H), 7.84 (td, $J = 6.24$ Hz, 8.60 Hz, 1H), 8.16 (d, $J = 1.74$ Hz, 8.76 Hz, 1H), 8.21 (d, $J = 8.88$ Hz, 1H), 8.23 (d, $J = 2.24$ Hz, 1H), 8.89 (d, $J = 1.80$ Hz, 1H), 8.75 (s, 1H), 8.94 (d, $J = 4.44$ Hz, 1H).

Example 20 N-(2-chloro-5-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)-2,4-difluorobenzenesulfonamide



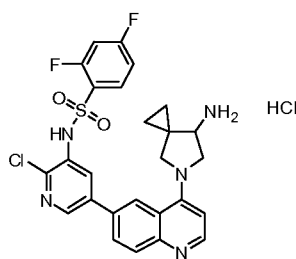
[0204] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinoline (0.6 g, 2.06 mmol), N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-2,4-difluorobenzene sulfonamide (0.56 g, 1.31 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (175 mg, 0.25 mmol) and Na_2CO_3 (0.6 g, 5.66 mmol) in DMF (8 mL) and H_2O (1 mL). The crude product was purified by a silica

gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (39 mg, 5.8%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 514 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.54 (s, 6H), 2.39 (s, 1H), 6.95-6.99 (m, 2H), 7.51-7.53 (m, 2H), 7.92-7.95 (m, 2H), 8.22 (d, $J = 8.8$ Hz, 1H), 8.40-8.45 (m, 1H), 8.53 (d, $J = 2.0$ Hz, 1H), 8.92 (d, $J = 4.8$ Hz, 1H).

Example 21 N-(5-(4-(7-amino-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)-2-chloropyridin-3-yl)-2,4-difluorobenzenesulfonamide hydrochloride



Step 1) 5-(6-bromoquinolin-4-yl)-N-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptan-7-amine

[0205] The title compound was prepared according to the procedure as described in **Example 4 Step 1** by using N-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptan-7-amine (0.64 g, 3 mmol) and 6-bromo-4-chloroquinoline (0.29 g, 1.2 mmol) in DMF (2 mL). The title compound was obtained as a pale yellow solid (0.33 g, 86.8%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 418 $[\text{M}+\text{H}]^+$.

Step 2) N-(5-(4-(7-((tert-butoxycarbonyl)amino)-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)-2-chloropyridin-3-yl)-2,4-difluorobenzenesulfonamide

[0206] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 5-(6-bromoquinolin-4-yl)-N-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptan-7-amine (0.86 g, 2.06 mmol), N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-2,4-difluorobenzenesulfonamide (0.56 g, 1.31 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (175 mg, 0.25 mmol) and Na_2CO_3 (0.6 g, 5.66 mmol) in DMF (8 mL) and H_2O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (98 mg, 11.8%). The title compound was characterized by LC-MS as shown below:

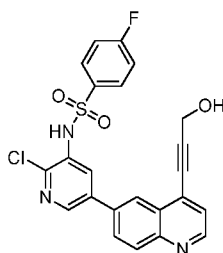
LC-MS (ESI, pos. ion) m/z: 641 [M+H]⁺.

Step 3) N-(5-(4-(7-amino-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)-2-chloropyridin-3-yl)-2,4-difluorobenzenesulfonamide hydrochloride

[0207] To a suspension of N-(5-(4-(7-((tert-butoxycarbonyl)amino)-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)-2-chloropyridin-3-yl)-2,4-difluorobenzenesulfonamide (50 mg, 80 μmol) in EtOAc (1 mL) was added a saturated solution of HCl in EtOAc (1 mL). The mixture was stirred at rt for 1 h then concentrated *in vacuo*. The residue solid was recrystallized in DCM (2 mL) to give the title compound as a light yellow solid (35 mg, 83.4%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 541 [M+H]⁺.

Example 22 N-(2-chloro-5-(4-(3-hydroxyprop-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide



Step 1) N-(5-bromo-2-chloropyridin-3-yl)-4-fluorobenzenesulfonamide

[0208] The title compound was prepared according to the procedure as described in **Example 1 Step 3** by using 5-bromo-2-chloropyridin-3-amine (6.43 g, 31 mmol) and 4-fluorobenzene-1-sulfonyl chloride (15.08 g, 77.5 mmol) in pyridine (25 mL). The title compound was obtained as a pale yellow solid (8.58 g, 75.7%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 365 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.16-7.21 (m, 2H), 7.81-7.85 (m, 2H), 8.14 (d, *J* = 2.4 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H).

Step 2) N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide

[0209] The title compound was prepared according to the procedure as described in **Example 1 Step 4** by using N-(5-bromo-2-chloropyridin-3-yl)-4-fluorobenzenesulfonamide (0.48 g, 1.31 mmol), bis(pinacolato)diboron (0.5 g, 1.97 mmol), PdCl₂(dppf)·CH₂Cl₂ (80 mg, 0.1

mmol) and KOAc (0.52 g, 5.24 mmol) in 1,4-dioxane (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (0.38 g, 67.8%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 413 [M+H]⁺.

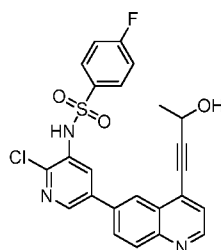
Step 3) N-(2-chloro-5-(4-(3-hydroxyprop-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)-4-fluorobenzene sulfonamide

[0210] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-hydroxyprop-1-yn-1-yl)quinoline (0.54 g, 2.06 mmol), N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide (0.54 g, 1.31 mmol), Pd(PPh₃)₂Cl₂ (175 mg, 0.25 mmol) and Na₂CO₃ (0.6 g, 5.66 mmol) in DMF (8 mL) and H₂O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (25 mg, 3.9%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 468 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.01 (s, 1H), 4.63 (s, 2H), 7.27-7.28 (m, 1H), 7.44-7.47 (m, 1H), 7.51-7.56 (m, 1H), 7.62-7.66 (m, 1H), 7.85-7.89 (m, 1H), 7.96-7.99 (m, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 2.4 Hz, 1H), 8.40 (d, *J* = 1.6 Hz, 1H), 8.53 (d, *J* = 2.4 Hz, 1H), 8.80 (d, *J* = 4.0 Hz, 1H).

Example 23 N-(2-chloro-5-(4-(3-hydroxybut-1-yn-1-yl)quinolin-6-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide



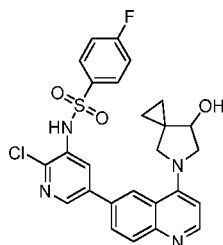
[0211] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 6-bromo-4-(3-hydroxybut-1-yn-1-yl)quinoline (0.57 g, 2.06 mmol), N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide (0.54 g, 1.31 mmol), Pd(PPh₃)₂Cl₂ (175 mg, 0.25 mmol) and Na₂CO₃ (0.6 g, 5.66 mmol) in DMF (8 mL) and H₂O (1 mL). The crude product was purified by a silica gel column

chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (30 mg, 4.7%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 482 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.68 (d, $J = 6.0$ Hz, 3H), 4.94-4.99 (m, 1H), 7.17-7.23 (m, 2H), 7.55-7.57 (m, 1H), 7.85-7.88 (m, 2H), 7.97-8.00 (m, 1H), 8.26 (d, $J = 8.8$ Hz, 1H), 8.46 (d, $J = 2.4$ Hz, 1H), 8.50 (d, $J = 2.0$ Hz, 1H), 8.56 (d, $J = 2.4$ Hz, 1H), 8.95 (d, $J = 4.4$ Hz, 1H).

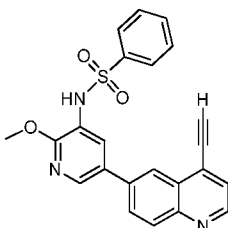
Example 24 N-(2-chloro-5-(4-(7-hydroxy-5-azaspiro[2.4]heptan-5-yl)quinolin-6-yl)pyridine-3-yl)-4-fluorobenzenesulfonamide



[0212] The title compound was prepared according to the procedure as described in **Example 1 Step 10** by using 5-(6-bromoquinolin-4-yl)-5-azaspiro[2.4]heptan-7-ol (0.66 g, 2.06 mmol), N-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-4-fluorobenzenesulfonamide (0.54 g, 1.31 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (175 mg, 0.25 mmol) and Na_2CO_3 (0.6 g, 5.66 mmol) in DMF (8 mL) and H_2O (1 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a light yellow solid (82 mg, 11.9%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z : 524 $[\text{M}+\text{H}]^+$.

Example 25 N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



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

[0213] To a suspension of 5-bromo-2-methoxypyridin-3-amine (2.51 g, 12.34 mmol) in pyridine (10 mL) was added benzenesulfonyl chloride (3.2 mL, 25 mmol). The reaction was stirred at rt for 22 h, then diluted with H_2O (100 mL). The resulting solid was collected by filtration, and was then washed with H_2O (10 mL). A suspension of the above solid and NaOH

(1.02 g, 25.5 mmol) in MeOH (20 mL) was stirred at rt for 2 h and then concentrated *in vacuo*. The mixture was diluted with DCM (20 mL) and 2M HCl (20 mL), then adjusted to pH 7 with 5% aq. NaHCO₃. The separated organic phase was dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound as yellow powder (3.92 g, 92.6%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 343 [M+H]⁺.

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

[0214] The title compound was prepared according to the procedure as described in **Example 1 Step 4** by using N-(5-bromo-2-methoxypyridin-3-yl)benzenesulfonamide (3.92 g, 11.42 mmol), bis(pinacolato)diboron (4.34 g, 17.09 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.95 g, 1.16 mmol) and KOAc (4.48 g, 45.64 mmol) in 1,4-dioxane (60 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as pale yellow powder (2.44 g, 54.8%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 391 [M+H]⁺.

Step 3) N-(2-methoxy-5-(4-((trimethylsilyl)ethynyl)quinolin-6-yl)pyridin-3-yl)benzene sulfonamide

[0215] The title compound was prepared according to the procedure as described in **Example 8 Step 2** by using 6-bromo-4-((trimethylsilyl)ethynyl)quinoline (0.43, 1.41 mmol), N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.55 g, 1.41 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.12 g, 0.15 mmol) and Na₂CO₃ (0.66 g, 6.23 mmol) in 1,4-dioxane (10 mL) and H₂O (2 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/3) to give the title compound as pale white powder (0.26 g, 37.8%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 488.2 [M+H]⁺.

Step 4) N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

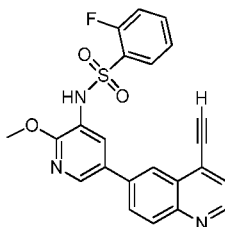
[0216] The title compound was prepared according to the procedure as described in **Example 8 Step 3** by using N-(2-methoxy-5-(4-((trimethylsilyl)ethynyl)quinolin-6-yl)pyridine-3-yl)benzene sulfonamide (0.26 g, 0.54 mmol) and KOH (0.11 g, 1.96 mmol) in a mixture of THF (5 mL) and MeOH (6 mL). The crude product was washed with MeOH (2 mL) to give the

title compound as a pale yellow crystal solid (0.18 g, 80.2%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 416 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 3.75 (s, 1H), 3.88 (s, 3H), 7.09 (s, 1H), 7.48 (m, 2H), 7.58 (m, 2H), 7.85 (m, 2H), 7.91 (dd, $J = 2.1$ Hz, 8.8 Hz, 1H), 8.20 (m, 3H), 8.38 (d, $J = 2.0$ Hz, 1H), 8.89 (d, $J = 4.4$ Hz, 1H).

Example 26 N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)-2-fluorobenzene-sulfonamide



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

[0217] The title compound was prepared according to the procedure as described in **Example 25 Step 1** by using 5-bromo-2-methoxypyridin-3-amine (2.5 g, 12.31 mmol) and 2-fluorobenzene-1-sulfonyl chloride (4.91 g, 25.1 mmol) in pyridine (10 mL). The title compound was obtained as yellow powder (3.94 g, 88.6%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z : 361 $[\text{M}+\text{H}]^+$.

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

[0218] The title compound was prepared according to the procedure as described in **Example 1 Step 4** by using N-(5-bromo-2-methoxypyridin-3-yl)-2-fluorobenzenesulfonamide (3.94 g, 10.94 mmol), bis(pinacolato)diboron (5.56 g, 21.89 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (0.93 g, 1.14 mmol) and KOAc (4.43 g, 45.14 mmol) in 1,4-dioxane (60 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/2) to give the title compound as pink powder (2.98 g, 66.7%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z : 409 $[\text{M}+\text{H}]^+$.

Step 3) 2-fluoro-N-(2-methoxy-5-(4-((trimethylsilyl)ethynyl)quinolin-6-yl)pyridin-3-yl)benzene sulfonamide

[0219] To a suspension of 6-bromo-4-((trimethylsilyl)ethynyl) quinoline (0.43 g, 1.41 mmol), 2-fluoro- N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl) benzenesulfonamide (0.58 g, 1.42 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (0.17 g, 0.21 mmol) in 1,4-dioxane (10 mL) and H_2O (2 mL) was added Na_2CO_3 (0.66 g, 6.23 mmol) under N_2 atmosphere. The reaction was stirred at 97°C for 40 min, then cooled down to rt, diluted with DCM (20 mL) and 5% aq. NaHCO_3 (10 mL). The separated organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/3) to give the title compound which was used in the next step directly. The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 506 $[\text{M}+\text{H}]^+$.

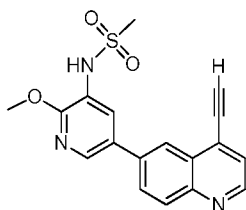
Step 4) N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)-2-fluorobenzenesulfonamide

[0220] The title compound was prepared according to the procedure as described in **Example 8 Step 3** by using 2-fluoro-N-(2-methoxy-5-(4-((trimethylsilyl)ethynyl)quinolin-6-yl)-pyridin-3-yl)benzenesulfonamide and KOH (0.17 g, 3.04 mmol) in a mixture of THF (5 mL) and MeOH (5 mL). The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as pale orange powder (73 mg, the total yield of the two steps was 11.9%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 434 $[\text{M}+\text{H}]^+$;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.69 (s, 3H), 4.12 (s, 1H), 7.35 (t, $J = 7.44$ Hz, 1H), 7.47 (t, $J = 10.0$ Hz, 1H), 7.74 (m, 3H), 7.95 (d, $J = 2.2$ Hz, 1H), 8.12 (m, 2H), 8.26 (d, $J = 1.6$ Hz, 1H), 8.45 (d, $J = 2.2$ Hz, 1H), 8.92 (d, $J = 4.4$ Hz, 1H), 10.33 (s, 1H).

Example 27 N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)methanesulfonamide



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

[0221] The title compound was prepared according to the procedure as described in **Example 25 Step 1** by using 5-bromo-2-methoxypyridin-3-amine (2.5 g, 12.31 mmol) and MsCl (2.81 g, 24.55 mmol) in pyridine (10 mL). The title compound was obtained as white powder

(2.46 g, 71.1%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z : 281 $[M+H]^+$.

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

[0222] The title compound was prepared according to the procedure as described in **Example 1 Step 4** by using N-(5-bromo-2-methoxypyridin-3-yl)methanesulfonamide (2.46 g, 8.78 mmol), bis(pinacolato)diboron (3.34 g, 13.15 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (0.72 g, 0.88 mmol) and KOAc (3.63 g, 36.99 mmol) in 1,4-dioxane (50 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/2) to give the title compound as white powder (1.72 g, 59.9%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z : 329 $[M+H]^+$.

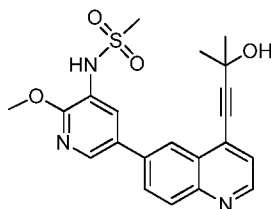
Step 3) N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)methanesulfonamide

[0223] The title compound was prepared according to the procedure as described in **Example 8 Step 2** by using 6-bromo-4-((trimethylsilyl)ethynyl)quinoline (0.46 g, 1.51 mmol), N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanesulfonamide (0.49 g, 1.5 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (0.12 g, 0.15 mmol) and Na_2CO_3 (0.64 g, 6.04 mmol) in 1,4-dioxane (10 mL) and H_2O (2 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/4) to give the title compound as white powder (0.14 g, 26.4%). The title compound was characterized by LC-MS and ^1H NMR as shown below:

LC-MS (ESI, pos. ion) m/z : 354 $[M+H]^+$;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.11 (s, 3H), 4.00 (s, 3H), 5.09 (s, 1H), 7.74 (d, $J = 3.9$ Hz, 1H), 8.02 (s, 1H), 8.16 (m, 2H), 8.33 (s, 1H), 8.46 (s, 1H), 8.92 (d, $J = 4.1$ Hz, 1H), 9.44 (s, 1H).

Example 28 N-(5-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinolin-6-yl)-2-methoxypyridin-3-yl)methanesulfonamide



[0224] The title compound was prepared according to the procedure as described in

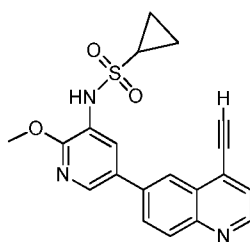
Example 8 Step 2 by using 6-bromo-4-(3-hydroxy-3-methylbut-1-yn-1-yl)quinoline (434 mg, 1.5 mmol), N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanesulfonamide (589 mg, 1.8 mmol), PdCl₂(dppf)·CH₂Cl₂ (184 mg, 0.23 mmol) and Na₂CO₃ (795 mg, 7.5 mmol) in 1,4-dioxane (15 mL) and H₂O (3 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) and then washed with MeOH (20 mL) to give the title compound as light pink powder (0.27 g, 44%). The title compound was characterized by LC-MS, ¹H NMR and ¹³C NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 412 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.74 (s, 6H), 3.08 (s, 3H), 3.13 (s, 1H), 4.08 (s, 3H), 6.92 (br.s, 1H), 7.45 (d, *J* = 4.48 Hz, 1H), 7.93 (dd, *J* = 8.76 Hz, 2.12 Hz, 1H), 8.16 (d, *J* = 8.76 Hz, 1H), 8.20 (d, *J* = 2.24 Hz, 1H), 8.30 (d, *J* = 2.24 Hz, 1H), 8.36 (d, *J* = 1.96 Hz, 1H), 8.36 (d, *J* = 4.48 Hz, 1H);

¹³C NMR (100MHz, CDCl₃) δ (ppm): 31.3, 39.9, 54.3, 65.7, 77.2, 104.9, 121.5, 123.5, 126.2, 128.0, 128.3, 129.6, 129.9, 130.5, 135.5, 140.1, 147.3, 149.8, 154.0.

Example 29 N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide



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

[0225] The title compound was prepared according to the procedure as described in **Example 25 Step 1** by using 5-bromo-2-methoxypyridin-3-amine (1.5 g, 7.39 mmol) and cyclopropanesulfonyl chloride (2.22 g, 14.82 mmol) in pyridine (6 mL). The title compound was obtained as white powder (2.04 g, 89.9%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 307 [M+H]⁺.

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

[0226] The title compound was prepared according to the procedure as described in **Example 1 Step 4** by using N-(5-bromo-2-methoxypyridin-3-yl)cyclopropanesulfonamide (2 g,

6.51 mmol), bis(pinacolato)diboron (2.48 g, 9.77 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.53 g, 0.65 mmol) and KOAc (2.72 g, 27.22 mmol) in 1,4-dioxane (50 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/2) to give the title compound as white powder (2.09 g, 90.62%). The title compound was characterized by LC-MS as shown below:

LC-MS (ESI, pos. ion) m/z: 355 [M+H]⁺.

Step 3) N-(5-(4-ethynylquinolin-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide

[0227] The title compound was prepared according to the procedure as described in **Example 8 Step 2** by using 6-bromo-4-((trimethylsilyl)ethynyl)quinoline (0.47, 1.55 mmol), N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)cyclopropane-sulfonamide (0.55 g, 1.55 mmol), PdCl₂(dppf)·CH₂Cl₂ (0.14 g, 0.17 mmol) and Na₂CO₃ (0.71 g, 6.7 mmol) in 1,4-dioxane (10 mL) and H₂O (2 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/3) to give the title compound as white powder (0.14 g, 23.8%). The title compound was characterized by LC-MS and ¹H NMR as shown below:

LC-MS (ESI, pos. ion) m/z: 380 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.02 (m, 2H), 1.25 (m, 2H), 2.55 (m, 1H), 3.73 (m, 1H), 4.10 (s, 3H), 6.82 (s, 1H), 7.59 (d, *J* = 4.4 Hz, 1H), 7.95 (dd, *J* = 2.1 Hz, 8.8 Hz, 1H), 8.19 (m, 2H), 8.33 (d, *J* = 2.2 Hz, 1H), 8.42 (d, *J* = 1.9 Hz, 1H), 8.89 (d, *J* = 4.4 Hz, 1H).

BIOLOGICAL TESTING

[0228] 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 of the present invention potentially inhibit PI3Ks and mTOR.

Example A

General Description for Kinase Assays

[0229] Kinase assays can be performed by measurement of incorporation of γ-³³P 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 3 x 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 MgCl₂, 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 and γ -³³P ATP is added to start the reaction (2×10^6 cpm of γ -³³P ATP per well (3000 Ci/mmol) and 10 μ M 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 μ L/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.

[0230] The above assay procedure can be used to determine the IC₅₀ for inhibition and/or the inhibition constant, K_i. The IC₅₀ is defined as the concentration of compound required to reduce the enzyme activity by 50% under the condition of the assay. The IC₅₀ value is estimated by preparing a 10 point curve using a $\frac{1}{2}$ log dilution series (for example, a typical curve may be prepared using the following compound concentrations: 10 μ M, 3 μ M, 1 μ M, 0.3 μ M, 0.1 μ M, 0.03 μ M, 0.01 μ M, 0.003 μ M, 0.001 μ M and 0 μ M).

PI3K p110 α /p85 α (m) [Non-radioactive assay]

[0231] PI3K p110 α /p85 α (m) is incubated in assay buffer containing 10 μ M 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 rt, 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 time-resolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula $HTRF = 10000 \times (Em_{665nm}/Em_{620nm})$.

mTOR (h)

[0232] 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 -³³P-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 μ L 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.

[0233] The kinase assays described herein were performed at Millipore UK Ltd, Dundee Technology Park, Dundee DD2 1SW, UK.

[0234] The compounds disclosed herein exhibited potent activities in the PI3K α (h) and mTOR (h) assays. Table 2 listed the IC₅₀s of some examples described herein in the PI3K α (h) and mTOR (h) assays.

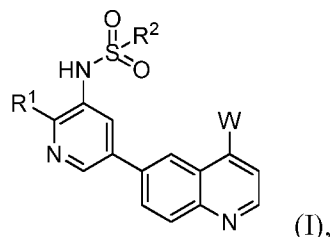
Table 2 Kinase inhibition data

Example #	IC ₅₀ (nM)	
	PI3K α (h)	mTOR (h)
1	3	26
2	6	/
3	5	15
4	21	/
5	17	/
6	23	/
7	29	/
10	7	/
12	19	/
24	3	/

[0235] 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):



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

W is D, CN, N₃, C₅₋₁₂spirobicycyl or $\{ \equiv X$; wherein the C₅₋₁₂spirobicycyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, -OR^a, -SR^a and -NR^aR^b;

X is H, D, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl) and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N₃, C₁₋₄alkyl, -OR^a, -SR^a and -NR^aR^b;

R¹ is H, D, Cl, -OR^a, C₁₋₆alkyl or C₃₋₆cycloalkyl, wherein each of the C₁₋₆alkyl and C₃₋₆cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, -OR^a, -SR^a and -NR^aR^b;

R² is C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, -(C₁₋₄alkylene)-(C₃₋₆cycloalkyl), -(C₁₋₄alkylene)-(C₃₋₆heterocyclyl), C₂₋₆alkenyl, C₂₋₆alkynyl, C₆₋₁₀aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N₃, -OR^a, -SR^a and -NR^aR^b; and

each R^a and R^b is independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected

from O, S and N, $-(C_{1-4}\text{alkylene})-(C_{3-6}\text{heterocyclyl})$, $-(C_{1-4}\text{alkylene})-(C_{6-10}\text{aryl})$ or $-(C_{1-4}\text{alkylene})-(5-10\text{ membered heteroaryl})$, 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.

2. The compound of claim 1, wherein W is CN, $C_{5-12}\text{spirobicyclyl}$ or $\text{---}\equiv\text{X}$, wherein the $C_{5-12}\text{spirobicyclyl}$ is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3 , $-\text{OR}^a$, $-\text{SR}^a$ and $-\text{NR}^a\text{R}^b$.

3. The compound of claim 1, wherein X is H, D, $C_{1-6}\text{alkyl}$, $C_{3-6}\text{cycloalkyl}$, $C_{3-6}\text{heterocyclyl}$, $-(C_{1-4}\text{alkylene})-(C_{3-6}\text{heterocyclyl})$ or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $C_{1-6}\text{alkyl}$, $C_{3-6}\text{cycloalkyl}$, $C_{3-6}\text{heterocyclyl}$, $-(C_{1-4}\text{alkylene})-(C_{3-6}\text{heterocyclyl})$ and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, $C_{1-3}\text{alkyl}$, $-\text{OR}^a$ and $-\text{NR}^a\text{R}^b$.

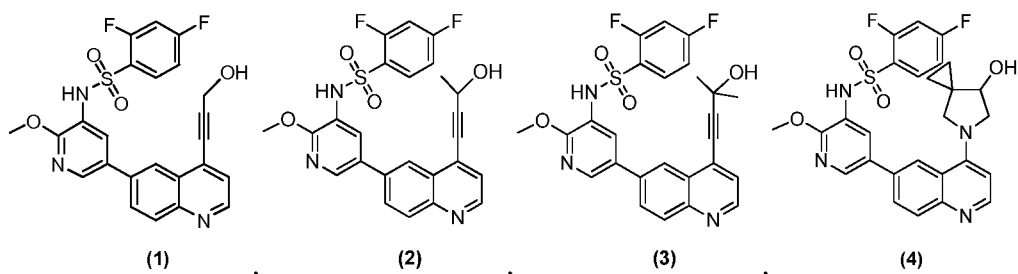
4. The compound of claim 1, wherein R^1 is H, D, Cl or $-\text{OR}^a$.

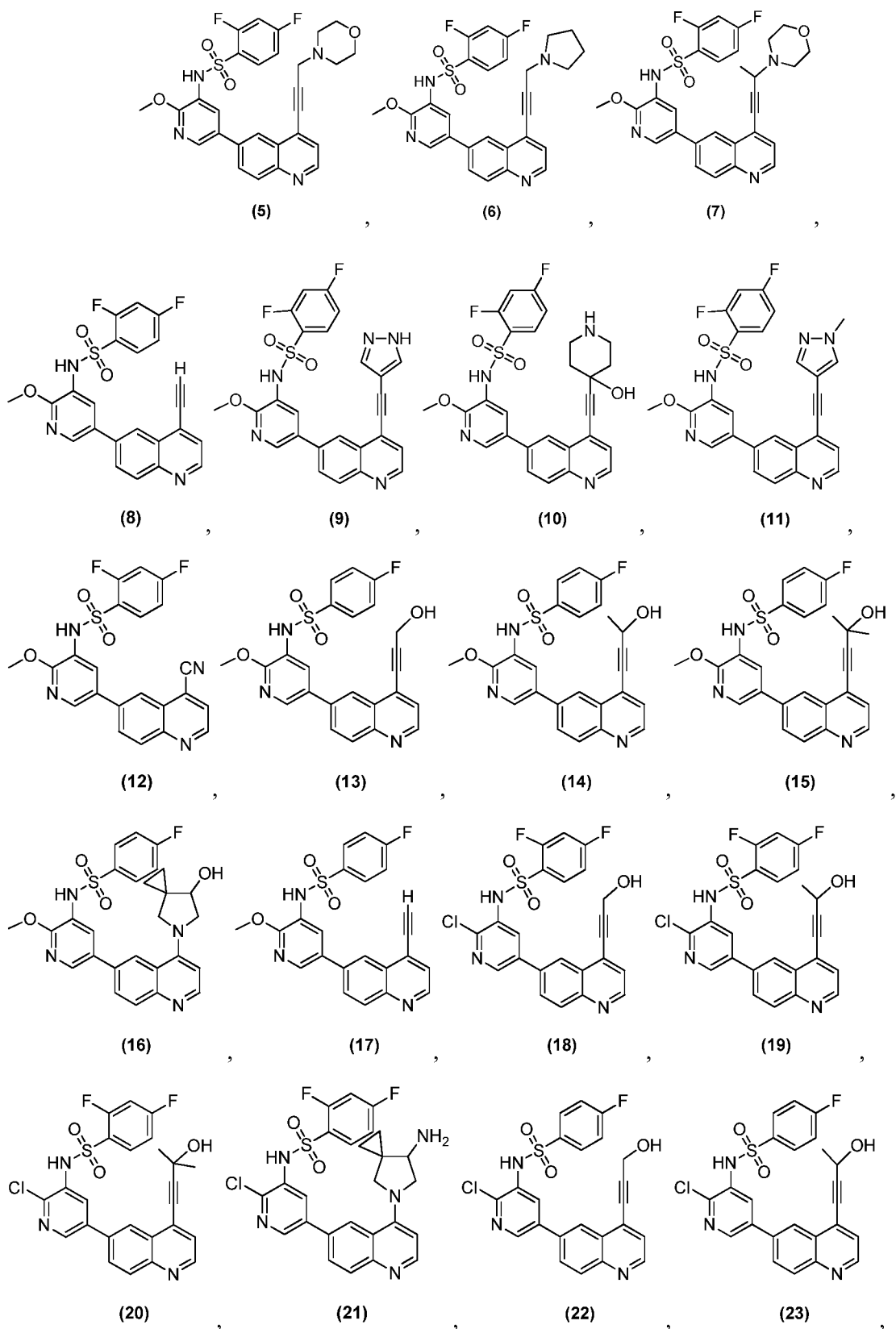
5. The compound of claim 1, wherein R^2 is $C_{1-6}\text{alkyl}$, $C_{3-6}\text{cycloalkyl}$ or $C_{6-10}\text{aryl}$, wherein each of the $C_{1-6}\text{alkyl}$, $C_{3-6}\text{cycloalkyl}$ and $C_{6-10}\text{aryl}$ is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F and Cl.

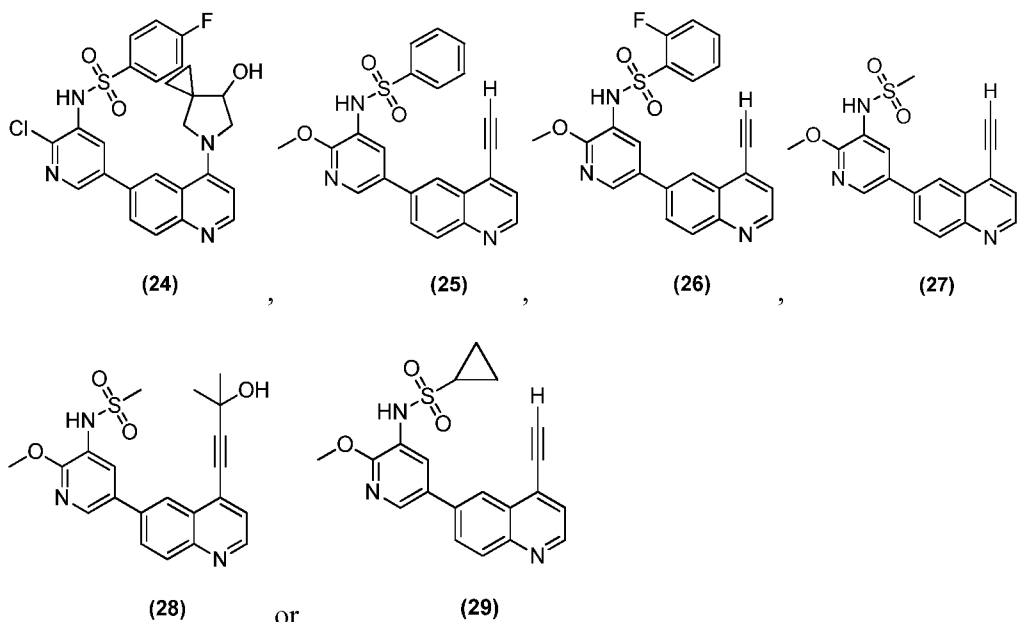
6. The compound of claim 1, wherein R^1 is Cl or OMe.

7. The compound of claim 1, wherein each R^a and R^b is independently H, $C_{1-3}\text{alkyl}$, $C_{1-3}\text{haloalkyl}$, $C_{3-6}\text{cycloalkyl}$, $C_{3-6}\text{heterocyclyl}$, $C_{6-10}\text{aryl}$, 5-10 membered heteroaryl comprising 1, 2, 3 and 4 heteroatoms independently selected from O, S and N, $-(C_{1-2}\text{alkylene})-(C_{3-6}\text{heterocyclyl})$, $-(C_{1-2}\text{alkylene})-(C_{6-10}\text{aryl})$ or $-(C_{1-2}\text{alkylene})-(5-10\text{ membered heteroaryl})$, 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.

8. The compound of claim 1 having one of the following structures:







9. A pharmaceutical composition comprising the compound of any one of claims 1 to 8, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

10. The pharmaceutical composition of claim 9 further comprising a therapeutic agent selected from the group consisting of chemotherapeutic agents, anti-proliferative agents, agents for treating atherosclerosis, agents for treating lung fibrosis and combinations thereof.

11. The pharmaceutical composition of claim 10, wherein the 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, prednisone, 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, brentuximabvedotin, catumaxomab, cetuximab, denosumab, gemtuzumab, ipilimumab, nimotuzumab, ofatumumab, panitumumab, ramucirumab, rituximab, tositumomab, trastuzumab, or a combination thereof.

12. The compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 11 for use in preventing, managing, treating or lessening the severity of a proliferative disorder in a patient.

13. A method of preventing, managing, treating or lessening the severity of a proliferative disorder in a patient by administering to the patient with the compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 11.

14. The compound or pharmaceutical composition of claim 12, wherein the proliferative disorder is metastatic cancer, 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, a myeloproliferative disorder, atherosclerosis or lung fibrosis.

15. The method of claim 13, wherein the proliferative disorder is metastatic cancer, 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, a myeloproliferative disorder, atherosclerosis or lung fibrosis.

16. A method of inhibiting or modulating the activity of phosphatidylinositol 3-kinases (PI3 kinases or PI3Ks) and/or mTOR in a biological sample comprising contacting a biological sample with the compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 11.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/51405

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/42; A61K 31/18, 31/47; C07D 401/04 (2013.01)

USPC - 546/1, 293; 514/253.06, 311, 314

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A01N 43/42; A61K 31/18, 31/47; C07D 401/04 (2013.01)

USPC: 546/1, 293; 514/253.06, 311, 314

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Reaxys; ProQuest; Google/Google Scholar; KEY WORDS: quinolin*, pyridin*, sulfonamide*, heterocycli*, aryl*, alkyl*, hetero*, spiro*, nitro*, cyano, sulf*, halo*, fluoro*, chloro*, bromo*, phosphatidylinositol, kinase, PI3K*, modulat*, signal* pathway, disorder*, disease*, cancer, chemotherapy*, proliferat*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	WO 2012/037108 A1 (BANKA, AL et al.) 22 March 2012; paragraph [00114], Table 1, compound 198	1-2, 4-8, 9/1-2, 9/4-8 ----- 3, 9/3, 10/9/1-8, 11/10/9/1-8
Y	TORBORG, C. et al. 'Improved Palladium-Catalyzed Sonogashira Coupling Reactions of Aryl Chlorides.' Chemistry - A European Journal, 2009, Vol 15, Issue 6, pages 1329-1336; Entry 4, Table 3, page 1332	3, 9/3, 10/9/3, 11/10/9/3
Y	US 2011/0092504 A1 (BO, YY et al.) 21 April 2011; examples 7, 12 and 26; paragraph [0423], [0427], [0527], [0537], [0577]	10/9/1-8, 11/10/9/1-8

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

09 December 2013 (09.12.2013)

Date of mailing of the international search report

16 DEC 2013

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Facsimile No. 571-273-3201

Authorized officer:

Shane Thomas

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 12-16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.