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(57) Abstract: The present invention provides novel substituted alkynyl compounds, pharmaceutical acceptable salts and formulations thereof useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion. The invention also provides pharmaceutically acceptable compositions comprising such compounds and methods of using the compositions in the treatment of hyperproliferative disorders in mammals, especially humans.



ALKYNYL COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial Number 61/734, 897, filed on December 07, 2012, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to novel substituted alkynyl compounds, and salts thereof, which are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals. In particular, the invention relates to compounds that inhibit the protein tyrosine kinase activity, resulting in the inhibition of inter- and/or intra-cellular signaling. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

Protein kinases are key regulators of cell function that constitute one of the largest and most functionally diverse gene families. By adding phosphate groups to substrate proteins, they direct the activity, localization and overall function of many proteins, and serve to orchestrate the activity of many cellular processes. Kinases are particularly prominent in signal transduction and co-ordination of complex functions such as the cell cycle. Of the 518 human protein kinases, 478 belong to a single superfamily whose catalytic domains are related in sequence. These can be clustered into groups, families and sub-families, of increasing sequence similarity and biochemical function.

A partial list of such kinases include abl, AATK, ALK, Akt, Axl, bmx, bcr-abl, Blk, Brk, Btk, csk, c-kit, c-Met, c-src, c-fins, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, DDR1, DDR2, EPHA, EPHB, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FER, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, GSG2, GSK, Hck, ILK, INSRR, IRAK4, ITK, IGF-1R, INS-R, Jak, KSR1, KDR, LMTK2, LMTK3, LTK, Lck, Lyn, MATK, MERTK, MLTK, MST1R, MUSK, NPR1, NTRK, MEK, MER, PLK4, PTK, p38, PDGFR, PIK, PKC, PYK2, RET, ROR1, ROR2, RYK, ros, Ron, SGK493, SRC, SRMS, STYK1, SYK, TEC, TEK, TEX14, TNK1, TNK2, TNKI3K, TXK, TYK2, Tyro-3, tie, tie2, TRK, Yes and Zap70.

Receptor tyrosine kinases (RTKs) are a diverse group of transmembrane proteins that act as receptors for cytokines, growth factors, hormones and other signaling molecules. Receptor

tyrosine kinases (RTKs) are expressed in many cell types and play important roles in a wide variety of cellular processes, including growth, differentiation and angiogenesis. Activation of the kinase is effected by binding of a ligand to the extracellular domain, which induces dimerization of the receptors. Activated receptors auto-phosphorylate tyrosine residues outside the catalytic domain via cross-phosphorylation. This auto-phosphorylation stabilizes the active receptor conformation and creates phosphotyrosine docking sites for proteins that transduce signals within the cell.

Receptor tyrosine kinases (RTKs) are hyper-activated (through receptor activating mutations, gene amplification, growth factor activation, etc.) in many human solid tumors and hematological malignancies. RTK's elevated activation contributes to tumourigenesis factors such as hyperplasia, survival, invasion, metastasis and angiogenesis. Inhibition of receptor tyrosine kinases proved to be effective strategies in cancer therapy (Sharma PS; et al. "Receptor tyrosine kinase inhibitors as potent weapons in war against cancers" *Curr. Pharm. Des.* **2009**, 15, 758).

Anaplastic lymphoma kinase (ALK), a membrane associated tyrosine kinase receptor from the insulin receptor superfamily, has been implicated in oncogenesis in several human tumors. Indeed, ALK was initially identified in constitutively activated and oncogenic fusion forms (the most common being nucleophosmin (NPM)-ALK) in a non-Hodgkin's lymphoma (NHL) known as anaplastic large-cell lymphoma (ALCL) (Morris, S. W.; et al. "Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma" *Science* **1994**, 263, 1281).

ALK fusions were also found in the human sarcomas called inflammatory myofibroblastic tumors (IMTs). Studies suggested that the ALK fusion, TPM4-ALK, may be involved in the genesis of a subset of esophageal squamous cell carcinomas. Moreover, studies have implicated various mutations of the ALK gene in both familial and sporadic cases of neuroblastoma. ALK mutations in neuroblastoma cells results in constitutive ALK phosphorylation and attenuation. Conversely, inhibition of ALK by sRNA and small molecule ALK inhibitors resulted in profound growth inhibition in those cell lines (Palmer, R. H.; et al. "Anaplastic lymphoma kinase: signalling in development and disease" *Biochem. J.* **2009**, 420, 345).

More recently, various isoforms of a fusion gene comprised of portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the ALK gene were identified in NSCLC cells. The EML4-ALK fusion transcript was detected in approximately 3-7% of NSCLC patients examined. Experimental evidence from in vitro and in vivo studies demonstrated oncogenic transforming activity of the EML4-ALK fusion proteins and reinforced the pivotal

role of EML4-ALK in the pathogenesis of NSCLC in humans (Soda, M.; et al. "Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer" *Nature* **2007**, 448, 561). Fusions of ALK have clear oncogenic potential as its aberrant tyrosine kinase activity enhances cell proliferation and survival and leads to cytoskeletal rearrangements and changes in cell shape. Oncogenic ALK transformation is mediated by interactions with downstream molecules that trigger substantial intracellular signaling cascades. Similarly to most normal and oncogenic tyrosine kinases, ALK fusions activate many different pathways that are strictly interconnected and overlapping. The most relevant and better characterized pathways are reported: the Ras-extracellular signal-regulated kinase (ERK) pathway, the Janus kinase 3 (JAK3)-STAT3 pathway and the phosphatidylinositol 3-kinase (PI3K)-Akt pathway. These three pathways have many points of interaction to mediate the effects of ALK activity. Overall, the JAK3-STAT3 pathway and the PI3K-Akt pathway have been shown to be vital primarily for cell survival and phenotypic changes (Chiarle, R.; et al. "The anaplastic lymphoma kinase in the pathogenesis of cancer" *Nat. Rev. Cancer* **2008**, 8, 11; Barreca, A.; et al. "Anaplastic lymphoma kinase (ALK) in human cancer" *J. Mol. Endocrinol.* **2011**, 47, R11).

The involvement of the full-length, normal ALK receptor in the genesis of additional malignancies including glioblastoma, neuroblastoma, breast cancer, and others has also been implicated. In a survey of a collection of human cancer cell lines, Dirks, et al. confirmed the expression of ALK transcripts in nervous system-derived lines, including retinoblastoma, and a large percentage of cell lines derived from solid cancers of ectodermal origin, including melanoma and breast carcinoma (Dirks, P. B. "Cancer's source in the peripheral nervous system" *Nature Medicine* **2008**, 14, 373).

c-Met, also referred to as hepatocyte growth factor receptor (HGFR), is expressed predominantly in epithelial cells but has also been identified in endothelial cells, myoblasts, hematopoietic cells and motor neurons. The natural ligand for c-Met is hepatocyte growth factor (HGF), also known as scatter factor (SF). In both embryos and adults, activated c-Met promotes a morphogenetic program, known as invasive growth, which induces cell spreading, the disruption of intercellular contacts, and the migration of cells towards their surroundings (Peschard P.; Park M. "From Tpr-Met to Met, tumorigenesis and tubes" *Oncogene* **2007**, 26, 1276; Stellrecht CM; Gandhi V. "Met Receptor Tyrosine Kinase as a Therapeutic Anticancer Target" *Cancer Letter* **2009**, 280, 1).

A wide variety of human malignancies exhibit sustained c-Met stimulation, overexpression, or mutation, including carcinomas of the breast, liver, lung, ovary, kidney, thyroid, colon, renal, glioblastomas, and prostate, etc. c-Met is also implicated in atherosclerosis and lung fibrosis.

Invasive growth of certain cancer cells is drastically enhanced by tumor-stromal interactions involving the HGF/c-Met pathway. Thus, extensive evidence that c-Met signaling is involved in the progression and spread of several cancers and an enhanced understanding of its role in disease have generated considerable interest in c-Met as major targets in cancer drug development (Migliore C.; Giordano S. "Molecular cancer therapy: can our expectation be MET" *Eur. J. Cancer* **2008**, 44, 641; Benedetta Peruzzi; Donald P. Bottaro. "Targeting the c-Met Signaling Pathway in Cancer" *Clinical Cancer Research* **2006**, 12, 3657). Agents targeting c-Met signaling pathway are now under clinical investigation (Joseph Paul Eder; et al. "Novel Therapeutic Inhibitors of the c-Met Signaling Pathway in Cancer" *Clinical Cancer Research* 2009, 15, 2207; Paolo M.; et al. "Drug development of MET inhibitors: targeting oncogene addiction and expedience" *Nature Review Drug Discovery* **2008**, 7, 504).

Many ALK and/or c-Met inhibitors are now under clinical development for the treatment of various human cancers. Crizotinib is an ATP-competitive small molecule ALK inhibitor, which also displays activity against the c-Met receptor tyrosine kinase. The FDA recently approved crizotinib (Pfizer's Xalkori[®], originally known as PF-02341066) for treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), in which tumor cells exhibit rearrangements in the anaplastic lymphoma kinase (ALK) gene. These rearrangements of the ALK gene (EML4-ALK) constitute driver mutations that are critical for the malignant phenotype of lung adenocarcinomas that have the mutations. Thus, the inhibition of mutated kinase ALK for the treatment of cancer is validated.

Crizotinib is administered 250 mg twice daily. Following oral single-dose administration, crizotinib was absorbed with median time to achieve peak concentration of 4 to 6 hours. Following crizotinib 250 mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8 (Xalkori[®] FDA-Approved Patient Labeling, Pfizer Inc. February 2012).

As seen with other targeted cancer drugs, patients with ALK-positive NSCLC eventually relapse on crizotinib. The development of acquired resistance is clearly the major hurdle preventing targeted therapies such as crizotinib from having an even more substantial impact on patients (*Nature Review Drug Discovery* **2011**, 10, 897).

There is, therefore, still a need for effective therapies for use in proliferative disease, including treatments for primary cancers, metastatic disease, and for targeted therapies, including tyrosine kinase inhibitors, such as ALK and/or c-Met inhibitors, dual inhibitors, selective inhibitors, and for potent, orally bioavailable, and efficacious inhibitors, and for inhibitors that provide

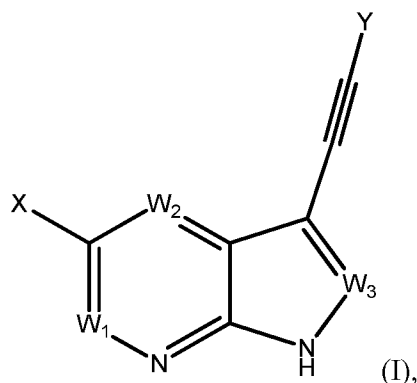
optimized dosing schedule, such as once daily oral administration.

The present invention provides novel compounds believed to have clinical use for treatment of cancer through inhibiting ALK and/or c-Met. Preferred compounds disclosed herein are also believed to provide an improvement in potency, pharmacokinetic properties, and/or toxicity profile over certain other ALK and/or c-Met inhibitor compounds found in the art.

SUMMARY OF THE INVENTION

Provided herein are new compounds and methods for treating cell proliferative diseases. The compounds disclosed herein are inhibitors of protein tyrosine kinases. Preferably, the compounds disclosed herein are capable of inhibiting, for example, ALK (including ALK fusions such as EML4-ALK, NPM-ALK, etc.), and c-Met receptor (hepatocyte growth factor receptor) signaling. Accordingly, provided herein are new inhibitors of protein tyrosine kinase receptor signaling, for example, ALK receptor signaling, c-Met receptor signaling.

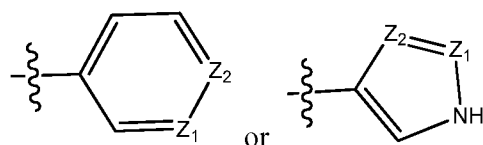
Specifically, it has been found that compounds disclosed herein, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of receptor tyrosine kinases such as ALK and c-Met. Accordingly, the invention provides compounds having the formula (I):



or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, wherein each of X, W₁, W₂, W₃ and Y is as defined herein.

In certain embodiments, each of W₁, W₂ and W₃ is independently N or CR^c;

X is



optionally substituted by one, two or three R¹ groups;

each of Z₁ and Z₂ is independently N or CH;

each R¹ is independently -D, -F, -Cl, -Br, -I, -CN, -NO₂, -N₃, -OR^a, -SR^a, -NR^aR^b, -(C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-NR^aR^b, -(C₁-C₄)alkylene-OR^a, -(C₃-C₁₀)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₁₀)cycloalkyl, -(C₃-C₁₀)heterocyclyl, -(C₁-C₄)alkylene-(C₃-C₁₀)heterocyclyl, -(C₆-C₁₀)aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatom(s) independently selected from O, S or N, -(C₁-C₄)alkylene-(C₆-C₁₀)aryl, or -(C₁-C₄)alkylene-(5-10 membered heteroaryl), with the proviso wherein Z₁ and Z₂ are CH, each of R¹ is not -OR^a or -NR^aR^b;

each hydrogen in R¹ is optionally substituted by R², and R¹ groups on adjacent atoms may combine to form a -(C₄-C₁₀)cycloalkyl, or (C₃-C₁₀)heterocyclyl, wherein the -(C₄-C₁₀)cycloalkyl, and -(C₃-C₁₀)heterocyclyl are optionally substituted by one, two, three or four R² groups;

each R² is independently -D, -F, -Cl, -Br, -I, -CN, -NO₂, -N₃, -OR^a, -SR^a, -NR^aR^b, -(C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-NR^aR^b, -(C₁-C₄)alkylene-OR^a, -(C₃-C₈)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, -(C₃-C₈)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₈)heterocyclyl;

Y is -(C₆-C₁₀)aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatom(s) independently selected from O, S or N, wherein the -(C₆-C₁₀)aryl, and 5-10 membered heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents independently selected from -D, -F, -Cl, -Br, -I, -CN, -NO₂, -N₃, -OR^a, -SR^a, -S(=O)R^a, -SO₂R^a, -NR^aR^b, -SO₂NR^aR^b, -OC(=O)R^a, -(C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-OR^a, -(C₃-C₈)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, -(C₃-C₈)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₈)heterocyclyl;

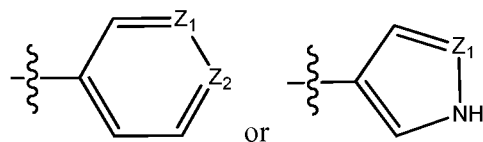
each of R^a and R^b is independently -H, -(C₁-C₆)aliphatic, -(C₃-C₆)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₆)heterocyclyl, wherein the -(C₁-C₆)aliphatic, -(C₃-C₆)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, and -(C₁-C₄)alkylene-(C₃-C₆)heterocyclyl are optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -Cl, -CN, -N₃, -OH, -NH₂, (C₁-C₆)alkoxy or (C₁-C₆)alkylamino;

R^c is -H, -D, -F, -Cl, -Br, -I, -N₃, -CN, -NH₂, -NHSO₂(C₁-C₆)alkyl, -NR^aC(=O)(C₁-C₆)alkyl, -NHC(=O)NR^aR^b, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkylamino, -(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, -(C₆-C₁₀)aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S or N, wherein the -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkylamino, -(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, -(C₆-C₁₀)aryl and 5-10 membered

heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents independently selected from -D, -F, -Cl, -CN, -N₃, -OH, -NH₂, -(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, -(C₁-C₆)haloalkyl, -(C₁-C₆)alkoxy, or -(C₁-C₆)alkylamino.

In another embodiment, W₁ and W₂ are CR^c, W₃ is N or CR^c.

In another embodiment, X is



optionally substituted by one, two or three R¹ groups, wherein each of Z₁ and Z₂ is independently N or CH.

In another embodiment, each R¹ is independently -D, -F, -Cl, -OR^a, -NR^aR^b, -(C₁-C₄)alkyl, -(C₁-C₄)haloalkyl, -(C₂-C₄)alkenyl, -(C₁-C₂)alkylene-NR^aR^b, -(C₁-C₂)alkylene-OR^a, -(C₃-C₆)cycloalkyl, -(C₁-C₂)alkylene-(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, or -(C₁-C₂)alkylene-(C₃-C₆)heterocyclyl, with the proviso wherein Z₁ and Z₂ are CH, each of R¹ is not -OR^a or -NR^aR^b;

each hydrogen in R¹ is optionally substituted by R², and R¹ groups on adjacent atoms may combine to form a -(C₅-C₆)cycloalkyl or (C₃-C₆)heterocyclyl, wherein the -(C₅-C₆)cycloalkyl, and -(C₃-C₆)heterocyclyl are optionally substituted by one, two, three or four R² groups.

In another embodiment, each R² is independently -D, -F, -Cl, -OR^a, -NR^aR^b, -(C₁-C₄)alkyl, -(C₁-C₄)haloalkyl, -(C₂-C₆)alkenyl, -(C₁-C₂)alkylene-NR^aR^b, -(C₁-C₂)alkylene-OR^a, -(C₃-C₆)cycloalkyl, -(C₁-C₂)alkylene-(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, or -(C₁-C₂)alkylene-(C₃-C₆)heterocyclyl.

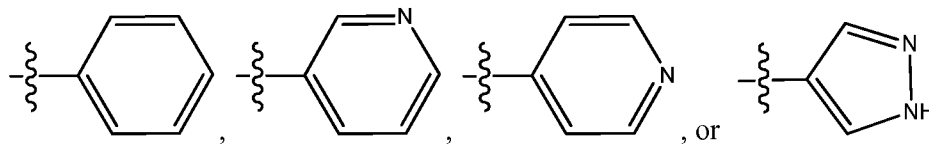
In another embodiment, Y is a phenyl group optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -Cl, -Br, -(C₁-C₃)alkyl, -(C₁-C₃)haloalkyl, or -(C₂-C₆)alkynyl.

In another embodiment, each of R^a and R^b is independently -H, -(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, or -(C₃-C₆)heterocyclyl, wherein the -(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, and -(C₃-C₆)heterocyclyl are optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -N₃, -OH, -NH₂, -(C₁-C₃)alkoxy, or -(C₁-C₃)alkylamino.

In another embodiment, R^c is -H, -D, -F, -Cl, -Br, -I, -N₃, -CN, -NH₂, -NHSO₂(C₁-C₃)alkyl, -NR^aC(=O)(C₁-C₃)alkyl, -NHC(=O)NR^aR^b, -(C₁-C₃)alkyl, -(C₁-C₃)alkoxy, -(C₁-C₃)alkylamino, -(C₃-C₆)cycloalkyl, or -(C₃-C₆)heterocyclyl, wherein the -(C₁-C₃)alkyl, -(C₁-C₃)alkoxy, -(C₁-

(C₃)alkylamino, -(C₃-C₆)cycloalkyl, and -(C₃-C₆)heterocyclyl are optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -Cl, -CN, -N₃, -OH, -NH₂, -(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, -(C₁-C₃)haloalkyl, -(C₁-C₃)alkoxy, or -(C₁-C₃)alkylamino.

In another embodiment, X is



optionally substituted by one, two, or three R¹ groups, and each hydrogen in R¹ is optionally substituted by R²; R¹ groups on adjacent atoms may combine to form a -(C₄-C₆)heterocyclyl, wherein the -(C₄-C₆)heterocyclyl is optionally substituted by one, two, three or four R² groups.

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 an inhibitor of protein tyrosine kinase. In other embodiments, the compound is an inhibitor of ALK receptor signaling and HGF receptor signaling.

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.

In certain embodiments, the therapeutic agent is adriamycin, rapamycin, temsirolimus, everolimus, ixabepilone, gemcitabin, cyclophosphamide, dexamethasone, etoposide, fluorouracil, afatinib, alisertib, amuvatinib, axitinib, bosutinib, brivanib, cabozantinib, cediranib, crenolanib, crizotinib, dabrafenib, dacomitinib, dasatinib, danusertib, dovitinib, erlotinib, foretinib, ganetespib, gefitinib, ibrutinib, imatinib, iniparib, lapatinib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, niraparib, nilotinib, 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, an interferon, carboplatin, topotecan, taxol, vinblastine, vincristine, temozolomide, tositumomab, trabectedin, belimumab, bevacizumab, brentuximab, cetuximab, gemtuzumab, ipilimumab, ofatumumab, panitumumab, ranibizumab, rituximab, tositumomab, trastuzumab or a combination thereof.

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 a compound disclosed herein, or the pharmaceutical composition disclosed herein to the patient.

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.

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.

In another aspect, provided herein is a method of inhibiting or modulating the activity of a protein kinase in a biological sample comprising contacting a biological sample with the compound disclosed herein, or the pharmaceutical composition disclosed herein.

In some embodiments, the protein kinase is a receptor tyrosine kinase. In other embodiments, the receptor tyrosine kinase is ALK and/or c-Met.

In another aspect, provided herein is a method of inhibiting protein tyrosine kinase, the method comprises contacting the kinase with the compound disclosed herein, or with the composition disclosed herein. In other embodiments, provided herein is a method of inhibiting ALK receptor signaling and/or HGF receptor signaling, the method comprises contacting the receptor with the compound disclosed herein, or with the pharmaceutical composition disclosed herein.

In some embodiments, inhibition of receptor protein kinase activity, such as ALK and/or HGF receptor signaling, can be in a cell or a multicellular organism. If in a multicellular organism, the method disclosed herein may comprise administering to the organism the compound disclosed herein, or the pharmaceutical composition disclosed herein. In some embodiments, the organism is a mammal; in other embodiments, the organism is a human. In still other embodiments, the method further comprises contacting the kinase with an additional therapeutic agent.

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.

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 disclose herein. In other embodiments, the method further comprises administering an additional therapeutic agent.

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 a compound disclosed herein or a composition thereof. In other embodiments, the method further comprises administering an additional therapeutic agent.

In another aspect, provided herein include methods of preparing, methods of separating, and methods of purifying compounds of Formula (I).

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

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.

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

As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994.

Additionally, general principles of organic chemistry are described in "Organic Chemistry" Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry" by Michael B. Smith and Jerry March, John Wiley & Sons, New York: 2007, the entire contents of which are hereby incorporated by reference.

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

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

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

The present invention also includes isotopically-labelled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Some non-limiting examples of isotopes that can be incorporated into the compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{16}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl .

[001] The compounds disclosed herein that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds disclosed herein, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

[002] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active

compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

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

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

Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, atropisomers 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. It is intended that all stereoisomeric forms of the compounds disclosed herein, including but not limited to, diastereomers, enantiomers, atropisomers, and geometric (or conformational) isomers as well as mixtures thereof such as racemic mixtures, form part of the present invention.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol

and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

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

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

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

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

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

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

The term "aliphatic" or "aliphatic group" as used herein, refers to a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. In some embodiments, aliphatic groups contain 1-10 carbon atoms. In other embodiments, aliphatic groups contain 1-8 carbon atoms. In still other embodiments, aliphatic groups contain 1-6 carbon atoms. In yet other embodiments, aliphatic groups contain 1-4 carbon atoms, and in further embodiments, aliphatic groups contain 1-3 carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. For example, (C₁-C₆)aliphatic groups include unbranched or branched, unsubstituted or suitably substituted (C₁-C₆)alkyl, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl groups.

The term "alkyl" or "alkyl group" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of 1 to 20 carbon atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described herein. Unless otherwise specified, alkyl groups contain 1-20 carbon atoms. In some embodiments, alkyl groups contain 1-10 carbon atoms. In other embodiments, alkyl groups contain 1-8 carbon atoms. In still other embodiments, alkyl groups contain 1-6 carbon atoms. In yet other embodiments, alkyl groups contain 1-4 carbon atoms, and in further embodiments, alkyl groups contain 1-3 carbon atoms.

Examples of alkyl groups include, but are not limited to, 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, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2-butyl (s-Bu, s-butyl, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-\text{C}(\text{CH}_3)_3$), 1-pentyl (n-pentyl, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-pentyl ($-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$), 3-pentyl ($-\text{CH}(\text{CH}_2\text{CH}_3)_2$), 2-methyl-2-butyl ($-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$), 3-methyl-2-butyl ($-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$), 3-methyl-1-butyl ($-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2-methyl-1-butyl ($-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1-hexyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-hexyl ($-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3-hexyl ($-\text{CH}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3)$), 2-methyl-2-pentyl ($-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3-methyl-2-pentyl ($-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 4-methyl-2-pentyl ($-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3-methyl-3-pentyl ($-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_3)_2$), 2-methyl-3-pentyl ($-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}(\text{CH}_3)_2$), 2,3-dimethyl-2-butyl ($-\text{C}(\text{CH}_3)_2\text{CH}(\text{CH}_3)_2$), 3,3-dimethyl-2-butyl ($-\text{CH}(\text{CH}_3)\text{C}(\text{CH}_3)_3$), 1-heptyl, 1-octyl, and the like.

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

The term "alkylene", as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms. Unless otherwise specified, alkylene groups contain 1-6 carbon atoms. In some embodiments, alkylene groups contain 1-4 carbon atoms. In other embodiments, alkylene groups contain 1-2 carbon atoms. Examples of alkylene groups include, but are not limited to, methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), isopropylene ($-\text{CH}(\text{CH}_3)\text{CH}_2-$), and the like.

The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Preferably, alkenyl group contains 2 to 8 carbon atoms, more preferably, 2 to 6 carbon atoms, and most preferably 2 to 4 carbon atoms. Examples include, but are not limited to, ethylenyl or vinyl ($-\text{CH}=\text{CH}_2$), allyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), and the like.

The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. Preferably, alkynyl group contains 2 to 8 carbon atoms, more preferably 2 to 6 carbon atoms, and most preferably 2 to 4 carbon atoms. Examples include, but are not limited to, ethynyl ($-\text{C}\equiv\text{CH}$), propynyl (propargyl, $-\text{CH}_2\text{C}\equiv\text{CH}$), $-\text{C}\equiv\text{C}-\text{CH}_3$, and the like.

The term "alkoxy" as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon atom through an oxygen atom. Unless otherwise specified, alkoxy groups

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

Examples of alkoxy groups include, but are not limited to, methoxy (MeO, -OCH₃), ethoxy (EtO, -OCH₂CH₃), 1-propoxy (n-PrO, n-propoxy, -OCH₂CH₂CH₃), 2-propoxy (i-PrO, i-propoxy, -OCH(CH₃)₂), 1-butoxy (n-BuO, n-butoxy, -OCH₂CH₂CH₂CH₃), 2-methyl-1-propoxy (i-BuO, i-butoxy, -OCH₂CH(CH₃)₂), 2-butoxy (s-BuO, s-butoxy, -OCH(CH₃)CH₂CH₃), 2-methyl-2-propoxy (t-BuO, t-butoxy, -OC(CH₃)₃), 1-pentoxy (n-pentoxy, -OCH₂CH₂CH₂CH₂CH₃), 2-pentoxy (-OCH(CH₃)CH₂CH₂CH₃), 3-pentoxy (-OCH(CH₂CH₃)₂), 2-methyl-2-butoxy (-OC(CH₃)₂CH₂CH₃), 3-methyl-2-butoxy (-OCH(CH₃)CH(CH₃)₂), 3-methyl-1-butoxy (-OCH₂CH₂CH(CH₃)₂), 2-methyl-1-butoxy (-OCH₂CH(CH₃)CH₂CH₃), and the like.

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

The term "carbocycle", "carbocyclyl", "carbocyclic ring" and "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. Suitable cycloaliphatic groups include, but are not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl. Further non-limiting 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, bicyclic, or tricyclic ring system. A bicyclic ring system includes a spiro bicyclyl or a fused bicyclyl. In some embodiments, a cycloalkyl contains 3 to 10 carbon atoms. In still other embodiments, a cycloalkyl contains 3 to 8 carbon atoms, and in yet other embodiments, a cycloalkyl contains 3 to 6 carbon atoms. The cycloalkyl radicals are optionally substituted independently with one or more substituents described herein.

[003] The term "heterocycle", "heterocyclyl" or "heterocyclic" as used interchangeably herein refers to a monocyclic, bicyclic, or tricyclic ring system in which one or more ring members are independently selected from heteroatoms and that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has one or more point of attachment to the rest of the molecule. A bicyclic ring system includes a spiro bicyclyl or a fused bicyclyl, and one of the rings can be either a monocarbocycle or a monoheterocycle. One or

more ring atoms are optionally substituted independently with one or more substituents described herein. In some embodiments, the "heterocycle", "heterocyclyl", or "heterocyclic" group is a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO₂, PO or PO₂). In other embodiments, it is a monocycle having 3 to 6 ring members (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or 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).

The heterocyclyl may be a carbon radical or heteroatom radical. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homo-piperazinyl, 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, pyrazolidinylimidazoliny, imidazolidiny, 1,2,3,4-tetrahydro iso-quinoliny. Some non-limiting examples of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidindionyl and 1,1-dioxo-thiomorpholiny.

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

The term "halogen" means fluoro (F), chloro (Cl), bromo (Br) or iodo (I).

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

The term "D" or "²H" denotes a single deuterium atom. One of this radical may be attached, for example, to a methyl group to form a mono-deuterated methyl group (-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).

The term "N₃" denotes 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 (PhN_3).

The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy" or "aryloxyalkyl" refers to monocyclic, bicyclic, and tricyclic carbocyclic ring systems having a total of 6 to 14 ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3-7 ring members and that has one or more point of attachment to the rest of the molecule. The term "aryl" may be used interchangeably with the term "aryl ring". Some non-limiting examples of aryl rings would include phenyl, naphthyl, and anthracene. The aryl radicals are optionally substituted independently with one or more substituents described herein.

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

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

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2\text{H}$. The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes $-(\text{C}=\text{O})-$.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups

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

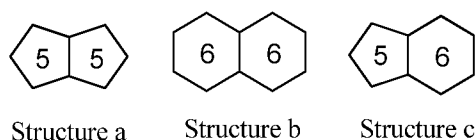
The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having 1 to 6 carbon atoms and one or more amino radicals. Some non-limiting examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl.

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

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

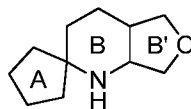
The terms "fused bicyclic", "fused cyclic", "fused bicycyl" or "fused cyclyl" refer to saturated bridged ring system which has a C-C bond shared between two five-membered rings (Structure a), two six-membered rings (Structure b) and one five-membered ring and one six-membered ring (Structure c), as depicted in Structures a-c. Each cyclic ring in a fused bicycyl can be either a carbocyclic or a heterocyclic.



Some non-limiting examples of fused bicyclic ring system include hexahydrofuro[3,2-*b*]furan, hexahydrofuro[2,3-*b*]furan, octahydrocyclopenta[*c*]pyrrole, hexahydro-1*H*-pyrrolizine, octahydro-1*H*-pyrido[1,2-*a*]pyrazine.

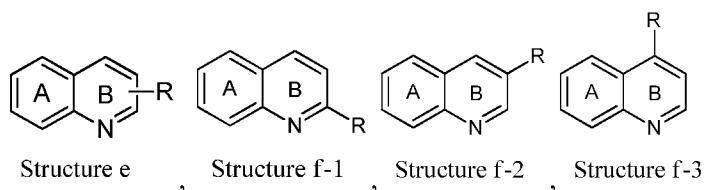
The terms "spirocyclyl", "spirocyclic", "spiro bicycyl" or "spiro bicyclic" refer to a ring originating from a particular annular carbon of another ring. For example, as depicted in Structure d, a saturated bridged ring system (ring B and B') is termed as "fused bicyclic";

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 can be either a carbocyclic or a heterocyclic.



Structure d

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 e represents possible substitution in any of the positions on the B ring shown in Structure f-1, f-2 and f-3.



The term "prodrug" as used herein, represents a compound that is transformed *in vivo* into a compound of formula (I). Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C₁-C₂₄) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound disclosed herein that contains an OH group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, for example those phosphates resulting from the phosphonation of an OH group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, J. Rautio et al, Prodrugs: Design and Clinical Applications, Nature Review Drug Discovery, 2008, 7, 255-270, and S. J. Hecker et al, Prodrugs of Phosphates and Phosphonates, Journal of Medicinal Chemistry, 2008, 51, 2328-2345, each of which is incorporated herein by reference.

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 disclosed herein, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

A "pharmaceutically acceptable salt" as used herein, refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* **1977**, 66, 1-19, which is incorporated herein by reference. Examples of pharmaceutically acceptable, nontoxic salts include, but are not limited to, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ 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.

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

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents,

antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

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

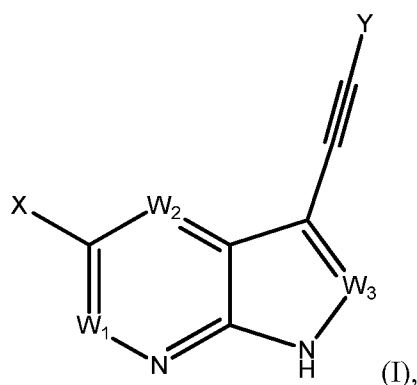
As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat",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

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 T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, **1991** and P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, **2005**.

DESCRIPTION OF THE COMPOUNDS DISCLOSED HEREIN

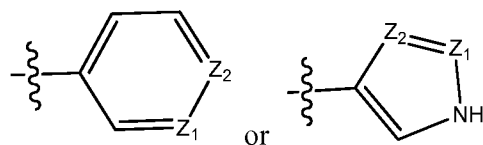
Provided herein are alkynyl compounds, salts, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and disorders modulated by receptor tyrosine kinases, especially ALK and c-Met receptor. More specifically, the present invention provides a compound of Formula (I):



or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, wherein each of X, W₁, W₂, W₃ and Y is as defined herein.

In certain embodiments, each of W₁, W₂ and W₃ is independently N or CR^c;

X is



optionally substituted by one, two or three R¹ groups;

each of Z₁ and Z₂ is independently N or CH;

each R¹ is independently -D, -F, -Cl, -Br, -I, -CN, -NO₂, -N₃, -OR^a, -SR^a, -NR^aR^b, -(C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-NR^aR^b, -(C₁-C₄)alkylene-OR^a, -(C₃-C₁₀)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₁₀)cycloalkyl, -(C₃-C₁₀)heterocyclyl, -(C₁-C₄)alkylene-(C₃-C₁₀)heterocyclyl, -(C₆-C₁₀)aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatom(s) independently selected from O, S or N, -(C₁-C₄)alkylene-(C₆-C₁₀)aryl, or -(C₁-C₄)alkylene-(5-10 membered heteroaryl), with the proviso wherein Z₁ and Z₂ are CH, each of R¹ is not -OR^a or -NR^aR^b;

each hydrogen in R¹ is optionally substituted by R², and R¹ groups on adjacent atoms may combine to form a -(C₄-C₁₀)cycloalkyl, or (C₃-C₁₀)heterocyclyl, wherein the -(C₄-C₁₀)cycloalkyl, and -(C₃-C₁₀)heterocyclyl are optionally substituted by one, two, three or four R² groups;

each R² is independently -D, -F, -Cl, -Br, -I, -CN, -NO₂, -N₃, -OR^a, -SR^a, -NR^aR^b, -(C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-NR^aR^b, -(C₁-C₄)alkylene-OR^a, -(C₃-C₈)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, -(C₃-C₈)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₈)heterocyclyl;

Y is -(C₆-C₁₀)aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatom(s) independently selected from O, S or N, wherein the -(C₆-C₁₀)aryl, and 5-10 membered heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents independently selected from -D, -F, -Cl, -Br, -I, -CN, -NO₂, -N₃, -OR^a, -SR^a, -S(=O)R^a, -SO₂R^a, -NR^aR^b, -SO₂NR^aR^b, -OC(=O)R^a, -(C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-OR^a, -(C₃-C₈)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, -(C₃-C₈)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₈)heterocyclyl;

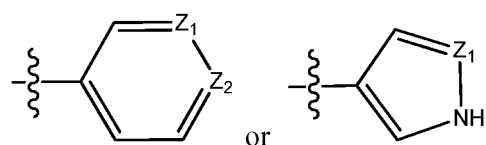
each of R^a and R^b is independently -H, -(C₁-C₆)aliphatic, -(C₃-C₆)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₆)heterocyclyl, wherein the -(C₁-C₆)aliphatic, -(C₃-C₆)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, and -(C₁-C₄)alkylene-(C₃-C₆)heterocyclyl are optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -Cl, -CN, -N₃, -OH, -NH₂, (C₁-C₆)alkoxy or (C₁-C₆)alkylamino;

R^c is -H, -D, -F, -Cl, -Br, -I, -N₃, -CN, -NH₂, -NHSO₂(C₁-C₆)alkyl, -NR^aC(=O)(C₁-C₆)alkyl, -NHC(=O)NR^aR^b, -(C₁-C₆)alkyl, -(C₁-C₆)alkoxy, -(C₁-C₆)alkylamino, -(C₃-C₆)cycloalkyl, -(C₃-C₆)heterocyclyl, -(C₆-C₁₀)aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms

independently selected from O, S or N, wherein the $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkoxy$, $-(C_1-C_6)alkylamino$, $-(C_3-C_6)cycloalkyl$, $-(C_3-C_6)heterocyclyl$, $-(C_6-C_{10})aryl$ and 5-10 membered heteroaryl are optionally substituted with 1, 2, 3 or 4 substituents independently selected from -D, -F, -Cl, -CN, -N₃, -OH, -NH₂, $-(C_1-C_6)alkyl$, $-(C_3-C_6)cycloalkyl$, $-(C_1-C_6)haloalkyl$, $-(C_1-C_6)alkoxy$, or $-(C_1-C_6)alkylamino$.

In certain embodiments, W₁ and W₂ are CR^c, W₃ is N or CR^c.

In another embodiment, X is



optionally substituted by one, two or three R¹ groups, wherein each of Z₁ and Z₂ is independently N or CH.

In another embodiment, each R¹ is independently -D, -F, -Cl, -OR^a, -NR^aR^b, $-(C_1-C_4)alkyl$, $-(C_1-C_4)haloalkyl$, $-(C_2-C_4)alkenyl$, $-(C_1-C_2)alkylene-NR^aR^b$, $-(C_1-C_2)alkylene-OR^a$, $-(C_3-C_6)cycloalkyl$, $-(C_1-C_2)alkylene-(C_3-C_6)cycloalkyl$, $-(C_3-C_6)heterocyclyl$, or $-(C_1-C_2)alkylene-(C_3-C_6)heterocyclyl$, with the proviso wherein Z₁ and Z₂ are CH, each of R¹ is not -OR^a or -NR^aR^b;

each hydrogen in R¹ is optionally substituted by R², and R¹ groups on adjacent atoms may combine to form a $-(C_5-C_6)cycloalkyl$ or $(C_3-C_6)heterocyclyl$, wherein the $-(C_5-C_6)cycloalkyl$, and $-(C_3-C_6)heterocyclyl$ are optionally substituted by one, two, three or four R² groups.

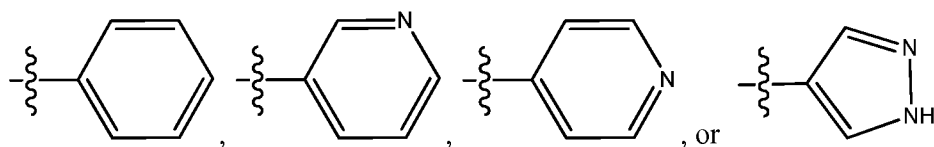
In another embodiment, each R² is independently -D, -F, -Cl, -OR^a, -NR^aR^b, $-(C_1-C_4)alkyl$, $-(C_1-C_4)haloalkyl$, $-(C_2-C_6)alkenyl$, $-(C_1-C_2)alkylene-NR^aR^b$, $-(C_1-C_2)alkylene-OR^a$, $-(C_3-C_6)cycloalkyl$, $-(C_1-C_2)alkylene-(C_3-C_6)cycloalkyl$, $-(C_3-C_6)heterocyclyl$, or $-(C_1-C_2)alkylene-(C_3-C_6)heterocyclyl$.

In another embodiment, Y is a phenyl group optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -Cl, -Br, $-(C_1-C_3)alkyl$, $-(C_1-C_3)haloalkyl$, or $-(C_2-C_6)alkynyl$.

In another embodiment, each of R^a and R^b is independently -H, $-(C_1-C_3)alkyl$, $-(C_3-C_6)cycloalkyl$, or $-(C_3-C_6)heterocyclyl$, wherein the $-(C_1-C_3)alkyl$, $-(C_3-C_6)cycloalkyl$, and $-(C_3-C_6)heterocyclyl$ are optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -N₃, -OH, -NH₂, $-(C_1-C_3)alkoxy$, or $-(C_1-C_3)alkylamino$.

In another embodiment, R^c is -H, -D, -F, -Cl, -Br, -I, -N₃, -CN, -NH₂, -NHSO₂(C₁-C₃)alkyl, -NR^aC(=O)(C₁-C₃)alkyl, -NHC(=O)NR^aR^b, -(C₁-C₃)alkyl, -(C₁-C₃)alkoxy, -(C₁-C₃)alkylamino, -(C₃-C₆)cycloalkyl, or -(C₃-C₆)heterocyclyl, wherein the -(C₁-C₃)alkyl, -(C₁-C₃)alkoxy, -(C₁-C₃)alkylamino, -(C₃-C₆)cycloalkyl, and -(C₃-C₆)heterocyclyl are optionally substituted with 1, 2, 3 or 4 substituent(s) independently selected from -D, -F, -Cl, -CN, -N₃, -OH, -NH₂, -(C₁-C₃)alkyl, -(C₃-C₆)cycloalkyl, -(C₁-C₃)haloalkyl, -(C₁-C₃)alkoxy, or -(C₁-C₃)alkylamino.

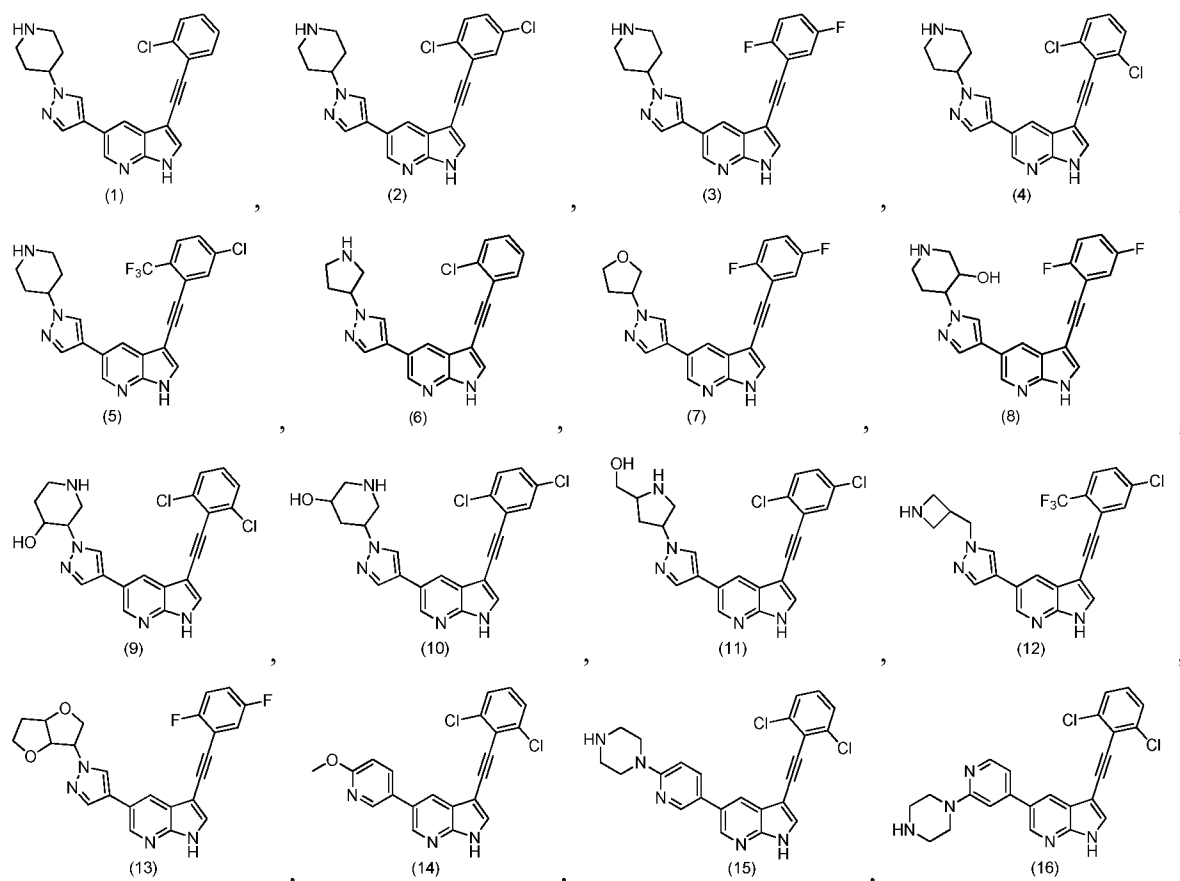
In another embodiment, X is

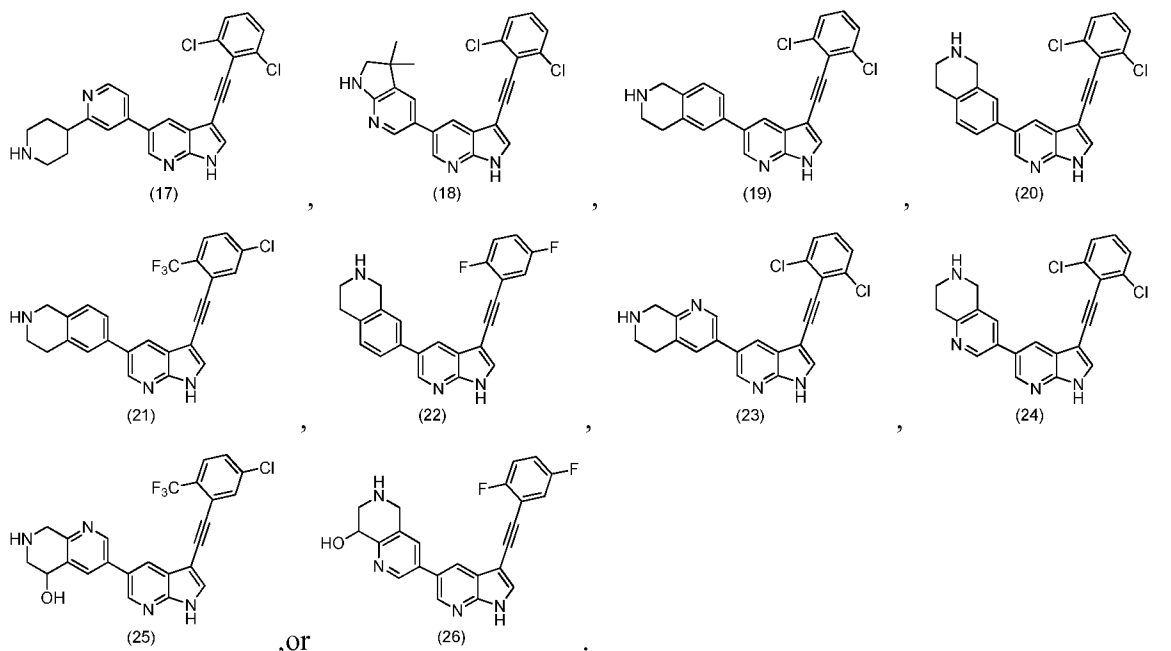


optionally substituted by one, two, or three R¹ groups, and each hydrogen in R¹ is optionally substituted by R²; R¹ groups on adjacent atoms may combine to form a -(C₄-C₆)heterocyclyl, wherein the -(C₄-C₆)heterocyclyl is optionally substituted by one, two, three or four R² groups.

Some non-limiting examples of the compound disclosed herein are shown in the following:

Table 1





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

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).

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

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.

The compounds disclosed herein 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).

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

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

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

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

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

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts disclosed herein can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions

are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

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

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

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

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I respectively.

In another aspect, the compounds disclosed herein include isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^3H , ^{14}C and ^{18}F , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single- photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled

compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O , acetone- d_6 , and DMSO- d_6 .

COMPOSITION, FORMULATIONS AND ADMINISTRATION OF THE COMPOUNDS DISCLOSED HEREIN

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

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

thereof.

As described above, the pharmaceutically acceptable compositions disclosed herein additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. In Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988- 1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, are disclosed various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds disclosed herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention.

Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as 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.

The compositions disclosed herein may be administered orally, parenterally, by inhalation spray,

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

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

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

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.

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.

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

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.

Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate,

propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

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.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. In order to prolong the effect of a compound disclosed herein, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, dissolving or suspending the compound in an oil vehicle accomplishes delayed absorption of a parenterally administered compound form.

Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Some non-limiting 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.

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.

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.

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

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 as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also

comprise buffering agents. They may optionally contain pacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Some non-limiting examples of embedding compositions that can be used include polymeric substances and waxes.

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.

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

The amount of the compounds disclosed herein 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.

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.

For example, chemotherapeutic agents or other antiproliferative agents may be combined with the compounds of this invention to treat proliferative disease or cancer. Examples of chemotherapeutic agents or other antiproliferative agents include HDAC inhibitors including, but are not limited to, SAHA, MS-275, MGO 103, and those described in WO 2006/010264, WO 03/024448, WO 2004/069823, US 2006/0058298, US 2005/0288282, WO 00/71703, WO 01/38322, WO 01/70675, WO 03/006652, WO 2004/035525, WO 2005/030705, WO 2005/092899, and demethylating agents including, but not limited to, 5-aza-dC, Vidaza and Decitabine and those described in US 6,268,137, 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.

In another embodiment of the present invention, for example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, for example, other therapies or anticancer agents that may be used in combination with the inventive anticancer agents disclosed herein and include surgery, radiotherapy (in but a few examples, gamma radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, taxanes (paclitaxel, taxotere), platinum derivatives (cisplatin, carboplatin, oxaliplatin), biologic response modifiers (interferons, interleukins), tumor necrosis factor (TNF, TRAIL receptor targeting agents, to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (chlormethine, chlorambucil, cyclophosphamide, ifosfamide, melphalan, etc), anti-metabolites (methotrexate, raltitrexed, pemetrexed, etc), purine antagonists and pyrimidine antagonists (6-mercaptopurine, 5-fluorouracil, cytarabine, gemcitabine), spindle poisons (vinblastine, vincristine, vinorelbine), podophyllotoxins (etoposide, irinotecan,

topotecan), antibiotics (doxorubicin, bleomycin, mitomycin), nitrosoureas (carmustine, lomustine), cell cycle inhibitors (KSP mitotic kinesin inhibitors, CENP-E and CDK inhibitors), enzymes (asparaginase), hormones (tamoxifen, leuprolide, flutamide, megestrol, dexamethasone), antiangiogenic agents (avastin and others), monoclonal antibodies (Belimumab (BENLYSTA[®]), brentuximab (ADCETRIS[®]), cetuximab (ERBITUX[®]), gemtuzumab (MYLOTARG[®]), ipilimumab (YERVOY[®]), ofatumumab (ARZERRA[®]), panitumumab (VECTIBIX[®]), ranibizumab (LUCENTIS[®]), rituximab (RITUXAN[®]), tositumomab (BEXXAR[®]), trastuzumab (HERCEPTIN[®]), kinase inhibitors (imatinib (GLEEVEC[®]), sunitinib (SUTENT[®]), sorafenib (NEXAVAR[®]), erlotinib (TARCEVA[®]), gefitinib (IRESSA[®]), dasatinib (SPRYCEL[®]), nilotinib (TASIGNA[®]), lapatinib (TYKERB[®]), crizotinib (XALKORI[®]), ruxolitinib (JAKAFI[®]), vemurafenib (ZELBORAF[®]), vandetanib (CAPRELSA[®]), pazopanib (VOTRIENT[®]), and others), and agents inhibiting or activating cancer pathways such as the mTOR, HIF (hypoxia induced factor) pathways (such as everolimus and temsirolimus) and others. For a more comprehensive discussion of updated cancer therapies see, <http://www.nci.nih.gov/>, a list of the FDA approved oncology drugs at <http://www.fda.gov/cder/cancer/druglist-rame.htm>, and The Merck Manual, Eighteenth Ed. 2006, the entire contents of which are hereby incorporated by reference.

In another embodiment, the compounds disclosed herein can be combined, with cytotoxic anti-cancer agents. Some non-limiting 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.

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

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

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

In another embodiment, the compounds disclosed herein can be combined with other signal transduction inhibitors. Some non-limiting examples of such agents include antibody therapies such as trastuzumab (HERCEPTIN[®]), cetuximab (ERBITUX[®]), ipilimumab (YERVOY[®]) and pertuzumab. Some non-limiting examples of such therapies also include 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.

In another embodiment, the compounds disclosed herein can be combined with inhibitors of histone deacetylase. Some non-limiting examples of such agents include suberoylanilide hydroxamic acid (SAHA), LAQ-824 (Ottmann, et al. Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3024), LBH-589 (Beck, et al. Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3025), MS-275 (Ryan, et al. Proceedings of the American Association of Cancer Research **2004**, 45, abstract 2452), FR-901228 (Piekarz, et al. Proceedings of the American Society for Clinical Oncology **2004**, 23, abstract 3028) and MGCD01 03 (US 6,897,220).

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

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.

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

USES OF THE COMPOUNDS AND COMPOSITIONS DISCLOSED HEREIN

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

The compounds disclosed herein would be useful for, but not limited to, the prevention or treatment of proliferative diseases, condition, or disorder in a patient by administering to the patient a compound or a composition disclosed herein in an effective amount. Such diseases,

conditions, or disorders include cancer, particularly metastatic cancer, atherosclerosis and lung fibrosis.

Compounds disclosed herein would be useful for the treatment of neoplasm including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute 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, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

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.

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

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

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.

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

The invention also features a method of inhibiting the growth of a cell that expresses ALK or c-Met, that includes contacting the cell with a compound or composition disclosed herein, thereby causing inhibition of growth of the cell. Some non-limiting examples of a cell whose growth can be inhibited include: a breast cancer cell, a colorectal cancer cell, a lung cancer cell, a papillary carcinoma cell, a prostate cancer cell, a lymphoma cell, a colon cancer cell, a pancreatic cancer cell, an ovarian cancer cell, a cervical cancer cell, a central nervous system cancer cell, an osteogenic sarcoma cell, a renal carcinoma cell, a hepatocellular carcinoma cell, a bladder cancer cell, a gastric carcinoma cell, a head and neck squamous carcinoma cell, a melanoma cell, or a leukemia cell.

The invention provides a method of inhibiting ALK or c-Met kinase activity in a biological sample that includes contacting the biological sample with a compound or composition disclosed herein. The term "biological sample" as used herein, means a sample outside a living organism and includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition of kinase activity, particularly ALK or c-Met kinase 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.

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 disclosed herein, 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.

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.

Suitable coatings and the general preparation of coated implantable devices are described in U.S. Patent Nos. 6,099,562; 5,886,026; and 5,304,121, the contents of each of which are incorporated by reference herein. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics into the composition. Implantable devices coated with a compound disclosed herein 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

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.

Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for formula (I), above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention. Persons skilled in the art will recognize that the chemical reactions described herein may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention

may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

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.

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.

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.

Column chromatography was conducted using a silica gel column. Silica gel (300 – 400 mesh) was purchased from Qingdao Ocean Chemical Factory. ^1H NMR spectra were recorded with a Bruker 400 MHz spectrometer or a Bruker 600 MHz spectrometer at ambient temperature. ^1H NMR spectra were obtained as CDCl_3 , $\text{DMSO}-d_6$, CD_3OD or acetone- d_6 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).

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).

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.

The following abbreviations are used throughout the specification:

ATP adenosine triphosphate

AcOH, HAc, CH₃COOH acetic acid

AIBN azodiisobutyronitrile

BBr₃ boron tribromide

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

BOC, Boc butyloxycarbonyl

BSA bovine serum albumin

n-BuOH butyl alcohol

n-BuLi *n*-butyllithium

CDCl₃ chloroform deuterated

CCl₄ carbon tetrachloride

CH₃COOK potassium acetate

CHCl₃ chloroform

CH₂Cl₂, DCM methylene chloride

CH₃SO₂Cl, MsCl methanesulfonyl chloride

Cs₂CO₃ cesium carbonate

Cu copper

CuI copper(I) 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

DME dimethoxyethane

DMF dimethylformamide

DMSO dimethylsulfoxide

DPPA diphenylphosphoryl azide

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

EtOAc, EA ethyl acetate

Et₂O diethyl ether

Et₃N, TEA triethylamine

FBS fetal bovine serum

Fe iron

g gram

h hour

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

HBr hydrobromic acid

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

HCl hydrochloric acid

H₂ hydrogen

H₂O water

H₂O₂ hydrogen peroxide

HOAc AcOH acetic acid

HOBt 1-hydroxybenzotriazole hydrate

K₂CO₃ potassium carbonate

KOH potassium hydroxide

LiHMDS lithium bis(trimethylsilyl)amide

LDA Lithium diisopropylamide

MCPBA *meta*-chloroperbenzoic acid

MeCN, CH₃CN acetonitrile

MeI methyl iodide

MeOH, CH₃OH methanol

2-MeTHF 2-methyl tetrahydrofuran

MgSO₄ magnesium sulfate

MsCl methanesulfonyl chloride

mL, ml milliliter

N₂ nitrogen

n-Bu₄NHSO₄ Tetrabutylammonium Hydrogen Sulfate

NaBH₄ sodium borohydride

NaBH₃CN Sodium cyanoborohydride

NaBH₃CN sodium cyanoborohydride

NaCl sodium chloride

NaClO₂ sodium chlorite

NaH sodium hydride
Na₂CO₃ sodium carbonate
NaHCO₃ sodium bicarbonate
NaH₂PO₄ sodium biphosphate
NaI sodium iodide
NaO(*t*-Bu) sodium *tert*-butoxide
NaOH sodium hydroxide
Na₂SO₄ sodium sulfate
NBS *N*-Bromosuccinimide
NIS *N*-Iodosuccinimide
NH₃ ammonia
NH₄Cl ammonium chloride
NMP *N*-methylpyrrolidinone
PBS phosphate buffered saline
P(*t*-Bu)₃ tri(*tert*-butyl)phosphine
Pd/C palladium on carbon
Pd₂(dba)₃ bis(dibenzylideneacetone) palladium
Pd(dppf)Cl₂ 1,1-bis(diphenylphosphino)ferrocene palladium chloride
Pd(dppf)Cl₂·CH₂Cl₂ dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
dichloromethane adduct
Pd(OAc)₂ palladium acetate
Pd(OH)₂ palladium hydroxide
Pd(PPh₃)₄ palladium tetrakis triphenylphosphine
Pd(PPh₃)₂Cl₂ Bis(triphenylphosphine)palladium(II) chloride
PE petroleum ether (60-90 °C)
POCl₃ phosphorous oxychloride
PhSO₂Cl benzenesulfonyl chloride
PyBop benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
RT, rt, r.t. room temperature
Rt retention time
TBAB tetrabutylammonium bromide
TBAF tetrabutyl ammonium fluoride
TBAHSO₄ tetrabutylammonium hydrogen sulfate
TBTU *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

TFA trifluoroacetic acid

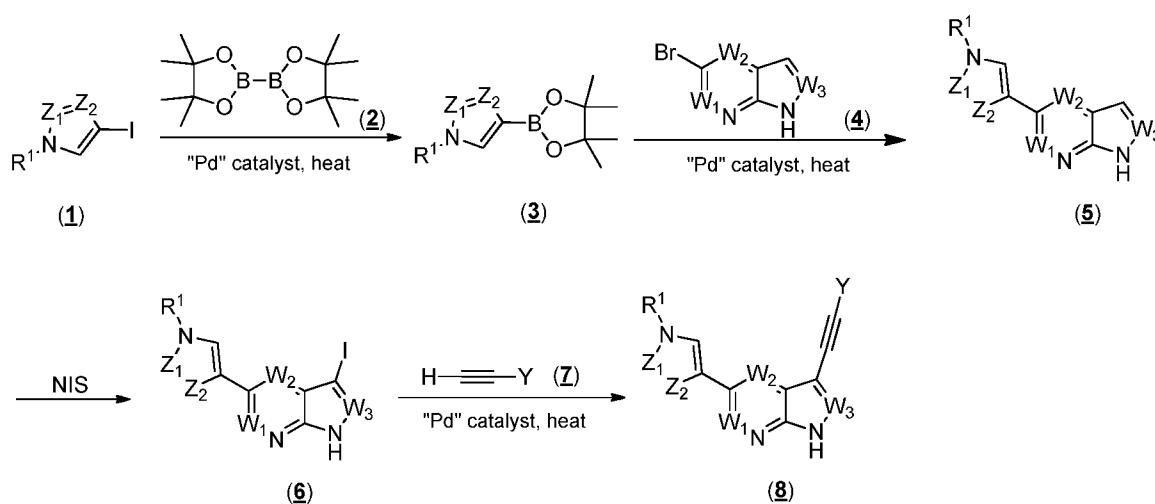
TEAC bis(*tetra*-ethylammonium)carbonate

THF tetrahydrofuran

μL microliter

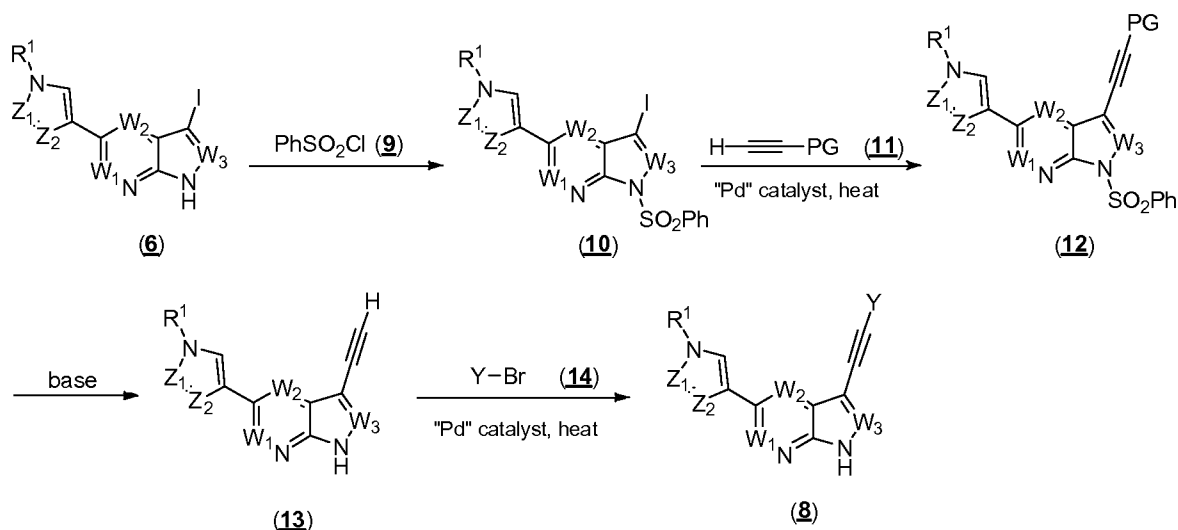
Representative synthetic procedures for the preparation of compounds of the disclosure are outlined below in following schemes. Unless otherwise indicated, W_1 , W_2 , W_3 , Z_1 , Z_2 , R^1 , and Y carry the definitions set forth above in connection with formula (I). "PG" is a suitable alkyne protecting group. Ring "A" is an optionally substituted N-containing heterocyclyl.

Scheme 1

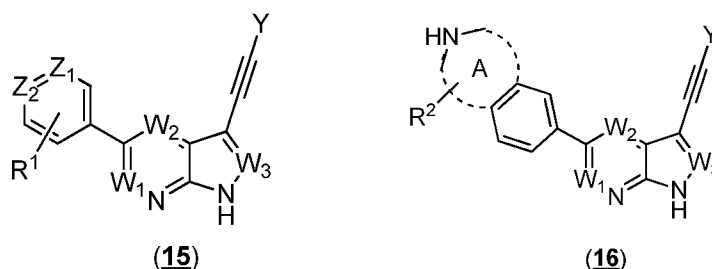


Some compounds with general structures as defined in Formula (I) can be prepared in a general method illustrated in Scheme 1. Compound (1) is first converted to boronic ester (or acid) (3) under standard conditions known to those skilled in the art such as, but not limited to, treatment with bis(pinacolato)diboron in the presence of Pd catalysis. Treatment of boronic ester (3) with bicyclic heteroaromatics (4) under Suzuki conditions gives compound (5). The subsequent iodination of (5) with N-iodosuccinimide affords iodo compound (6). The desired kinase inhibitors (8) are obtained by the coupling of iodo compound (6) with alkynyl compound (7) in the presence of an appropriate Pd catalyst.

Scheme 2



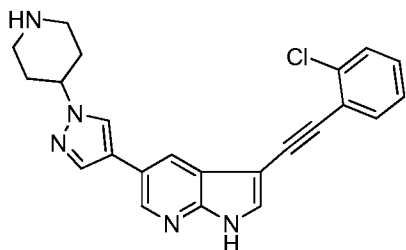
Alternatively, the compounds disclosed herein may be prepared by the method as described in Scheme 2. Compound **(6)** is protected with a suitable group such as, but not limited to, PhSO_2 , in the presence of PhSO_2Cl and base such as NaOH , Et_3N , or pyridine in an aprotic solvent (for example, CH_2Cl_2 , CHCl_3 , etc.). Compound **(10)** is then reacted with alkyne **(11)** under Sonogashira conditions to give compound **(12)**. Suitable alkyne protecting groups PG include, but are not limited to, TMS, TES or TIPS. The protecting groups PG can be removed under standard conditions known to those skilled in the art such as, but not limited to, treatment with aqueous base or TBAF to give compound **(13)**. Coupling of **(13)** with compound **(14)** in the presence of an appropriate Pd catalyst affords the desired kinase inhibitors **(8)**.



Kinase inhibitors **(15)** and **(16)** can also be prepared according to the general methods as described in Schemes 1 and 2.

EXAMPLES

Example 1 3-((2-chlorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine



Step 1) tert-butyl 4-(4-iodo-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (485 mg, 2.41 mmol) and DMAP (29.4 mg, 0.241 mmol) in DCM (15 mL) at 0 °C was added Et₃N (0.67 mL, 4.82 mmol) and MsCl (0.223 mL, 2.897 mmol) slowly. The mixture was stirred at rt for 5 hours, then diluted with 1 N aqueous NaHCO₃ (25 mL) and extracted with DCM (50 mL x 2). The combined organic phases were washed with brine (25 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue as the crude product was used in next step without purification.

To a solution of 4-iodo-1H-pyrazole (467.5 mg, 2.41 mmol) was added NaH (60%, 193 mg, 4.82 mmol) in dry DMF (8 mL) at 0 °C portion-wise, then warmed to rt and continued to stirred for 2 hours, followed by adding of a solution of the above product in DMF (4 mL). The mixture was heated at 100 °C for 12 hours, then quenched with NH₄Cl (aq, 20 mL) and extracted with EtOAc (40 mL x 2). The combined organic phases were washed with brine (25 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (620 mg, 68 %).

MS (ESI, pos. ion) m/z: 322.0 (M+1-56).

Step 2) tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (281.6 mg, 1.11 mmol) in DMSO (6 mL) was added tert-butyl 4-(4-iodo-1H-pyrazol-1-yl) piperidine-1-carboxylate (298.8 mg, 0.792 mmol), CH₃COOK (310.5 mg, 3.17 mol) and Pd(PPh₃)₂Cl₂ (33.36 mg, 0.0475 mmol) sequentially under nitrogen atmosphere. The mixture was stirred at 80 °C for 3 hours, then cooled to rt, quenched with H₂O (20 mL) and extracted with EtOAc (35 mL x 2). The combined organic phases were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (250 mg, 83%).

MS (ESI, pos. ion) m/z: 378.0 (M+1).

Step 3) tert-butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a stirred solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (197.0 mg, 1.0 mmol) and tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (453 mg, 1.2 mmol) in DME (25 mL) was added a solution of Na₂CO₃ (318 mg, 3.0 mmol) in water (2.5 mL). Then to the stirred solution that has been degassed with nitrogen for three times was added Pd(PPh₃)₂Cl₂ (70.2 mg, 0.1 mmol). The mixture was degassed and charged with nitrogen for three times again and refluxed for overnight, then cooled to rt, diluted with EtOAc (10 mL), filtered through celite pad and the precipitate was washed with EtOAc (15 mL). The filtrate was concentrated *in vacuo*, and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a pale solid (260 mg, 71%).

MS (ESI, pos. ion) m/z: 368.0 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.49 (s, 9H), 1.90-2.08 (m, 2H), 2.14-2.25 (m, 2H), 2.92 (t, *J* = 12.2 Hz, 2H), 4.20-4.42 (m, 3H), 6.51 (dd, *J* = 3.4 Hz, 1.6 Hz, 1H), 7.37 (dd, *J* = 3.2 Hz, 2.3 Hz, 1H), 7.70 (s, 1H), 7.83 (s, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 8.48 (d, *J* = 2.0 Hz, 1H), 10.45 (s, 1H);

¹³C NMR (400 MHz, CDCl₃): δ 28.6, 32.7, 59.7, 80.2, 101.0, 120.6, 121.2, 123.6, 126.0, 136.7, 141.1, 154.8.

Step 4) tert-butyl 4-(4-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (150 mg, 0.41 mmol) in acetone (6 mL) was added NIS (110 mg, 0.49 mmol). The mixture was stirred at rt for 2 hours. The precipitate was collected by filtration and washed with ice-cold acetone (10 mL) to give the title compound as a white solid (150 mg, 75%).

MS (ESI, pos. ion) m/z: 494.0 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.49 (s, 9H), 1.90-2.10 (m, 2H), 2.16-2.28 (m, 2H), 2.90-3.08 (m, 2H), 4.15-4.50 (m, 3H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.75 (s, 1H), 7.78 (d, *J* = 2.0 Hz, 1H), 7.85 (d, *J* = 0.5 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 10.19 (s, 1H).

Step 5) tert-butyl 4-(4-(3-((2-chlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a microwave vial was added tert-butyl 4-(4-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (600 mg, 1.22 mmol), 1-chloro-2-ethynylbenzene (0.178 mL, 1.46 mmol), CuI (3 mg, 0.016 mmol), Pd(PPh₃)₂Cl₂ (60 mg, 0.086 mmol), Et₃N (6 mL), and DMF (20 mL). The vial was capped and then stirred and heated under microwave conditions at

80 °C for 1 hour. The mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a yellow solid (300 mg, 49%).

MS (ESI, pos. ion) *m/z*: 502.0 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.43 (s, 9H), 1.76-1.91 (m, 2H), 2.02-2.11 (m, 2H), 2.80-3.10 (m, 2H), 4.00-4.12 (m, 2H), 4.32-4.48 (m, 1H), 7.41 (dd, *J* = 5.9 Hz, 3.5 Hz, 2H), 7.58-7.62 (m, 1H), 7.71-7.75 (m, 1H), 7.95 (d, *J* = 2.8 Hz, 1H), 7.99 (d, *J* = 0.4 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.39 (s, 1H), 8.62 (d, *J* = 2.0 Hz, 1H), 12.21 (d, *J* = 2.4 Hz, 1H).

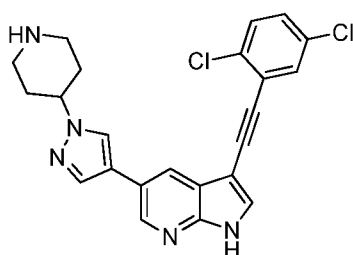
Step 6) 3-((2-chlorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine

To a stirred solution of tert-butyl 4-(4-(3-((2-chlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (300 mg, 0.60 mmol) in DCM (40 mL) was added a solution of HCl in EtOAc (4.3 mL, 12.9 mmol, 3 M) at 0 °C. The mixture was warmed to rt and continued to stirred for 4 hours, then concentrated *in vacuo*, and the residue was dissolved in water (100 mL). The aqueous phase was adjusted to PH = 10 with saturated aqueous Na₂CO₃ and extracted with DCM (100 mL x 5). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was washed with EtOAc (6 mL) to give the title compound as an off white solid (140 mg, 58%).

MS (ESI, pos. ion) *m/z*: 402.0 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 1.75-1.90 (m, 2H), 1.92-2.03 (m, 2H), 2.53-2.66 (m, 2H), 3.00-3.11 (m, 2H), 4.10-4.28 (m, 1H), 7.38-7.44 (m, 2H), 7.57-7.62 (m, 1H), 7.70-7.76 (m, 1H), 7.95 (s, 1H), 7.97 (s, 1H), 8.17 (d, *J* = 2.1 Hz, 1H), 8.34 (s, 1H), 8.61 (d, *J* = 2.1 Hz, 1H), 12.21 (s, 1H).

Example 2 3-((2,5-dichlorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine



Step 1) tert-butyl 4-(4-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(4-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (4.93 g, 10 mmol) in DCM (120 mL) was added PhSO₂Cl (2 mL, 15 mmol), *n*-Bu₄NHSO₄ (0.44 g, 1.29 mmol) and 50% aqueous NaOH (1.0 g, 25 mmol) respectively. The mixture was stirred at rt for 16 hours, then diluted with DCM (100 mL), washed with water (150 mL) and saturated aqueous NaHCO₃ (100 mL). The separated organic phase was dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as a white solid (6.1 g, 96%).

MS (ESI, pos. ion) *m/z*: 634.0 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.69 (d, *J*=2.0 Hz, 1H), 8.48 (s, 1H), 8.17-8.12 (m, 3H), 8.05 (d, *J*=0.4 Hz, 1H), 7.91 (d, *J*=2.1 Hz, 1H), 7.77-7.71 (m, 1H), 7.68-7.65 (m, 2H), 4.45-4.32 (m, 1H), 4.20-4.00 (m, 2H), 3.05-2.85 (br, 2H), 2.10-2.00 (m, 2H), 1.88-1.72 (m, 2H), 1.43 (s, 9H).

Step 2) tert-butyl 4-(4-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(4-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.8 g, 1.26 mmol) in DMF (15 mL) was added Pd(PPh₃)₂Cl₂ (44 mg, 0.063 mmol) and CuI (12 mg, 0.063 mmol). Then to the suspension that has been degassed with nitrogen for three times was added trimethyl silyl acetylene (0.13 g, 1.26 mmol) and Et₃N (3.50 mL, 25.25 mmol). The mixture was stirred at 75 °C under nitrogen atmosphere for 2 hours, then cooled to rt, diluted with DCM (150 mL), and washed with 5% aqueous NaHCO₃ (80 mL), water (80 mL) and brine (80 mL x 2). The separated organic phase was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a light yellow solid (0.6 g, 83%).

MS (ESI, pos. ion) *m/z*: 604.5 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 0.28 (s, 9H), 1.42 (s, 9H), 1.80 (m, 2H), 2.02 (m, 2H), 2.89 (s, 2H), 4.03 (m, 2H), 4.38 (m, 1H), 7.64 (t, *J*=8.1 Hz, 2H), 7.74 (t, *J*=7.5 Hz, 1H), 8.04 (s, 1H), 8.05 (d, *J*=2.1 Hz, 1H), 8.15 (m, 2H), 8.25 (s, 1H), 8.45 (s, 1H), 8.71 (d, *J*=2.1 Hz, 1H).

Step 3) tert-butyl 4-(4-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(4-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.76 g, 1.26 mmol) in MeOH (15 mL) was added KOH (0.14 g, 2.52 mmol). The mixture was stirred at rt for 2 hours, then washed with brine (60 mL), and extracted with DCM (50 mL x 3). The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a light yellow solid (0.17 g, 34%).

MS (ESI, pos. ion) m/z: 392.2 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.49 (s, 9H), 1.97 (m, 2H), 2.18 (m, 2H), 2.89 (m, 2H), 3.22 (s, 1H), 4.30 (m, 3H), 7.57 (d, *J*=2.3 Hz, 1H), 7.74 (s, 1H), 7.85 (d, *J*=0.6 Hz, 1H), 8.09 (d, *J*=2.0 Hz, 1H), 8.50 (d, *J*=2.0 Hz, 1H), 9.44 (s, 1H).

Step 4) tert-butyl 4-(4-(3-((2,5-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(4-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.20 g, 0.51 mmol) in DMF (15 mL) was added Pd(PPh₃)₂Cl₂ (36 mg, 0.051 mmol), CuI (10 mg, 0.051 mmol) and 1,4-dichloro-2-bromobenzene (0.12 g, 0.51 mmol). The mixture was degassed and charged with nitrogen for three times, then Et₃N (1.4 mL, 10.2 mmol) was added. The mixture was stirred at 75 °C for 2 hours. After the removal of the solvent, the residue was diluted with DCM (100 mL), and then washed with brine (100 mL x 2). 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) = 1/2) to give the title compound as a yellow solid (0.17 g, 62%).

MS (ESI, pos. ion) m/z: 536.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.42 (s, 9H), 1.86 (m, 2H), 2.04 (m, 2H), 2.95 (m, 2H), 4.05 (m, 2H), 4.39 (m, 1H), 7.47 (dd, *J*=8.7 Hz, 2.6 Hz, 1H), 7.61 (d, *J*=8.7 Hz, 1H), 7.83 (d, *J*=2.5 Hz, 1H), 7.97 (d, *J*=2.6 Hz, 1H), 8.01 (s, 1H), 8.21 (d, *J*=1.9 Hz, 1H), 8.39 (s, 1H), 8.62 (s, 1H), 12.27 (s, 1H).

Step 5) 3-((2,5-dichlorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine

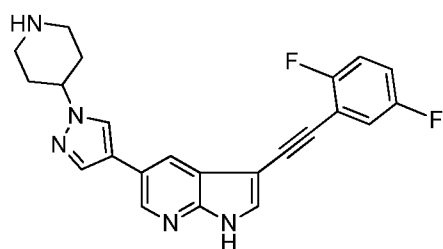
To a suspension of tert-butyl 4-(4-(3-((2,5-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.17 g, 0.32 mmol) in DCM (15 mL) was added a solution of HCl in EtOAc (3.20 mL, 12.8 mmol, 4 M). The mixture was stirred at rt for overnight.

After the removal of the solvent, the residue was adjusted to pH = 12 with saturated aqueous Na₂CO₃, then the mixture was extracted with DCM/MeOH (10/1, 50 mL x 3). The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was recrystallized by DCM (6 mL) to give the title compound as a light yellow solid (85 mg, 61%).

MS (ESI, pos. ion) m/z: 436.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.82 (m, 2H), 1.98 (m, 2H), 3.03 (m, 2H), 4.20 (m, 2H), 7.46 (dd, *J*=8.7 Hz, 2.5 Hz, 1H), 7.61 (d, *J*=8.7 Hz, 1H), 7.83 (d, *J*=2.5 Hz, 1H), 7.97 (d, *J*=3.5 Hz, 2H), 8.20 (d, *J*=1.9 Hz, 1H), 8.33 (s, 1H), 8.60 (d, *J*=1.8 Hz, 1H), 12.27 (s, 1H).

Example 3 3-((2,5-difluorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine



Step 1) tert-butyl 4-(4-(3-((2,5-difluorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a microwave vial was added tert-butyl 4-(4-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.1 g, 0.26 mmol), 2-bromo-1,4-difluorobenzene (58 mg, 0.26 mmol), Pd(PPh₃)₂Cl₂ (9.0 mg, 0.013 mmol), CuI (2.0 mg, 0.013 mmol), Et₃N (1 mL), and DMF (4 mL). The mixture was degassed and charged with nitrogen for three times. The vial was capped and then stirred and heated under microwave conditions at 120 °C for 30 minutes. Then the mixture was cooled to rt, diluted with DCM (100 mL), and washed with brine (100 mL x 3). 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) = 1/2) to give the title compound as a light yellow solid (0.14 g, 81%).

MS (ESI, pos. ion) m/z: 504.2 (M+1);

¹H NMR: (400 Hz, DMSO-*d*₆): δ 1.43 (s, 9H), 1.84 (m, 2H), 2.05 (m, 2H), 2.95 (s, 2H), 4.06 (m, 2H), 4.38 (m, 1H), 7.31 (m, 1H), 7.38 (m, 1H), 7.62 (m, 1H), 7.98 (d, *J*=2.8 Hz, 1H), 8.02 (s, 1H), 8.19 (d, *J*=1.8 Hz, 1H), 8.41 (s, 1H), 8.62 (d, *J*=1.8 Hz, 1H), 12.26 (s, 1H).

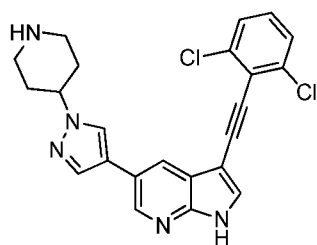
Step 2) 3-((2,5-difluorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine

The titled compound was prepared according to the procedure as described in Example 2 Step 5 by using a mixture of tert-butyl 4-(4-(3-((2,5-difluorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (140 mg, 0.28 mmol), and a solution of HCl in EtOAc (2.5 mL, 10 mmol, 4 M) in DCM (10 mL). The crude product was purified by a preparative HPLC (DCM/MeOH= 4/1) to give the title compound as a light yellow solid (30 mg, 26%).

MS (ESI, pos. ion) m/z: 404.2 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 1.98 (m, 2H), 2.10 (m, 2H), 2.19 (m, 2H), 3.05 (m, 2H), 4.46 (m, 1H), 5.32 (s, 1H), 7.31 (m, 1H), 7.39 (m, 1H), 7.61 (m, 1H), 7.99 (s, 1H), 8.07 (s, 1H), 8.21 (d, *J*=2.1 Hz, 1H), 8.38 (s, 1H), 8.63 (s, 1H), 12.26 (s, 1H).

Example 4 3-((2,6-dichlorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine



Step1) tert-butyl 4-(4-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 4-(4-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.10 g, 0.26 mmol), 1,3-dichloro-2-bromobenzene (57 mg, 0.26 mmol), Pd(PPh₃)₂Cl₂ (9 mg, 0.013 mmol), CuI (2 mg, 0.013 mmol), and Et₃N (1.43 mL, 10.2 mmol) in DMF (4 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a light yellow solid (0.07 g, 51%).

MS (ESI, pos. ion) m/z: 536.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.42 (s, 9H), 1.84 (m, 2H), 2.04 (m, 2H), 2.94 (m, 2H), 4.12 (m, 2H), 4.36 (m, 1H), 7.40 (t, *J*=8.3 Hz, 1H), 7.61 (d, *J*=8.1 Hz, 2H), 7.94 (s, 1H), 8.01 (d, *J*=2.7 Hz, 1H), 8.11 (d, 1H), 8.36 (s, 1H), 8.62 (m, 1H), 12.31 (s, 1H).

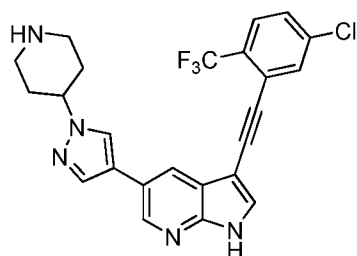
Step 2) 3-((2,6-dichlorophenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine

The titled compound was prepared according to the procedure as described in Example 2 Step 5 by using a mixture of tert-butyl 4-(4-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.13 g, 0.24 mmol), and a solution of HCl in EtOAc (2.50 mL, 10.0 mmol, 4 M) in DCM (10 mL). The crude product was recrystallized by DCM (6 mL) to give the title compound as a light yellow solid (85 mg, 80%).

MS (ESI, pos. ion) m/z: 436.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.81 (m, 2H), 1.97 (m, 2H), 3.03 (m, 2H), 4.21 (m, 2H), 7.39 (t, *J*=8.2 Hz, 1H), 7.60 (d, *J*=8.1 Hz, 2H), 7.92 (s, 1H), 8.01 (s, 1H), 8.10 (d, *J*=2.0 Hz, 1H), 8.30 (s, 1H), 8.61 (d, *J*=2.0 Hz, 1H).

Example 5 3-((5-chloro-2-(trifluoromethyl)phenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine



Step 1) 2-bromo-4-chloro-1-(trifluoromethyl)benzene

To a stirred solution of 40% HBr (2.20 mL, 15.34 mmol) in H₂O (2 mL) was added 2-amino-4-chlorobenzotrifluoride (0.50 g, 2.56 mmol) at 0 °C. Then a solution of sodium nitrite (0.21 g, 3.07 mmol) in H₂O (2 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for a further 0.5 hours, a solution of cuprous bromide (0.63 g, 4.35 mmol) in 40% HBr (2.20 mL, 15.34 mmol) and H₂O (3 mL) was added. The mixture was stirred at 75 °C for 3 hours, then cooled to rt, and extracted with EtOAc (40 mL x 4). The combined organic phases were washed with brine (80 mL x 2), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound as a yellow liquid (0.76 g, 100%).

GC -MS: 257.9.

Step 2) tert-butyl 4-(4-(3-((5-chloro-2-(trifluoromethyl)phenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of

tert-butyl 4-(4-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.30 g, 0.80 mmol), 2-bromo-4-chloro-1-(trifluoromethyl)benzene (0.62 g, 2.40 mmol), Pd(PPh₃)₂Cl₂ (28 mg, 0.04 mmol), CuI (7 mg, 0.04 mmol), and Et₃N (2.20 mL, 16.0 mmol) in DMF (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a yellow solid (0.38 g, 63%).

MS (ESI, pos. ion) m/z: 570.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.49 (s, 9H), 2.02 (m, 2H), 2.22 (m, 2H), 2.93 (m, 2H), 4.34 (m, 2H), 7.35 (dd, *J*=8.4 Hz, 1.1 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.65 (m, 2H), 7.75 (s, 1H), 7.88 (s, 1H), 8.15 (s, 1H), 8.52 (s, 1H).

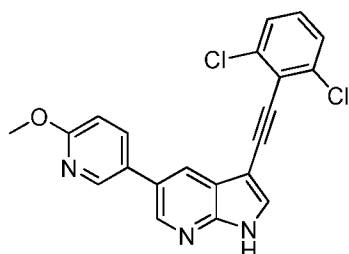
Step 3) 3-(((5-chloro-2-(trifluoromethyl)phenyl)ethynyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine

The titled compound was prepared according to the procedure as described in Example 2 Step 5 by using a mixture of tert-butyl 4-(4-(3-(((5-chloro-2-(trifluoromethyl)phenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.38 g, 0.67 mmol), and a solution of HCl in EtOAc (6.67 mL, 26.7 mmol, 4 M) in DCM (30 mL). The crude product was recrystallized by DCM (10 mL) to give the title compound as a yellow solid (0.17 g, 54%).

MS (ESI, pos. ion) m/z: 470.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 2.00 (m, 2H), 2.23 (m, 2H), 2.80 (m, 2H), 3.97 (m, 2H), 4.31 (m, 1H), 7.41 (m, 1H), 7.63 (s, 1H), 7.65 (m, 1H), 7.68 (s, 1H), 7.85 (s, 2H), 8.19 (d, *J*=2.0 Hz, 1H), 8.45 (d, *J*=1.9 Hz, 1H).

Example 6 3-(((2,6-dichlorophenyl)ethynyl)-5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine



Step 1) 5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

To a suspension of 2-methoxyl-5-bromopyridine (1.50 g, 7.98 mmol), Pd(dppf)₂Cl₂·CH₂Cl₂ (0.65 g, 0.80 mmol) and Cs₂CO₃ (7.80 g, 23.93 mmol) in DME/H₂O (5/1, 96 mL) was added 7-azaindole-5-boronic acid pinacol ester (2.92 g, 11.97 mmol). The mixture was degassed and

charged with nitrogen for three times, then refluxed for 4 hours. After the removal of the solvent, the residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (1.80 g, 95%).

MS (ESI, pos. ion) m/z : 226.1 (M+1);

^1H NMR (400 MHz, CDCl_3): δ 4.00 (s, 3H), 6.57 (d, $J=3.2$ Hz, 1H), 6.85 (d, $J=8.6$ Hz, 1H), 7.39 (d, $J=1.8$ Hz, 1H), 7.81 (dd, $J=8.5$ Hz, 2.52 Hz, 1H), 8.06 (d, $J=2.1$ Hz, 1H), 8.41 (d, $J=2.3$ Hz, 1H), 8.48 (d, $J=2.0$ Hz, 1H), 9.54 (s, 1H).

Step 2) 3-iodo-5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

To a stirred solution of 5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (1.0 g, 4.44 mmol) in acetone (20 mL) was added NIS (1.2 g, 5.33 mmol). The mixture was stirred at rt for 5 hours. After the removal of the most of acetone, the mixture was filtered, and the filter cake was washed with cold acetone to give the title compound as a white solid (1.35 g, 86%).

MS (ESI, pos. ion) m/z : 352.0 (M+1);

^1H NMR (400 MHz, CDCl_3): δ 4.00 (s, 3H), 6.87 (d, $J=8.6$ Hz, 1H), 7.48 (s, 1H), 7.83 (dd, $J=8.6$ Hz, 2.56 Hz, 1H), 7.87 (d, $J=2.0$ Hz, 1H), 8.42 (d, $J=2.2$ Hz, 1H), 8.47 (d, $J=2.0$ Hz, 1H), 9.40 (s, 1H).

Step 3) 3-iodo-5-(6-methoxypyridin-3-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine

To a suspension of 3-iodo-5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (0.12 g, 0.34 mmol), and $n\text{-Bu}_4\text{NHSO}_4$ (0.02 g, 0.2 mmol) in DCM (10 mL) was added PhSO_2Cl (0.07 mL, 0.51 mmol) and 50% aqueous NaOH (0.07 g, 0.85 mmol). The mixture was stirred at rt for 3 hours, then diluted with DCM (100 mL) and washed with 5% aqueous NaHCO_3 (100 mL x 2). The organic phase was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a light yellow solid (0.145 g, 94%).

MS (ESI, pos. ion) m/z : 491.9 (M+1);

^1H NMR (400 MHz, CDCl_3): δ 3.99 (s, 3H), 6.85 (d, $J=8.6$ Hz, 1H), 7.50 (t, $J=8.0$ Hz, 2H), 7.59 (t, $J=7.4$ Hz, 1H), 7.74 (d, $J=2.1$ Hz, 1H), 7.77 (dd, $J=8.6$ Hz, 2.5 Hz, 1H), 7.91 (s, 1H), 8.22 (d, $J=7.4$ Hz, 2H), 8.37 (d, $J=2.2$ Hz, 1H), 8.59 (d, $J=2.0$ Hz, 1H).

Step 4) 5-(6-methoxypyridin-3-yl)-1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridine

To a suspension of 3-iodo-5-(6-methoxypyridin-3-yl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (0.85 g, 2.42 mmol) and Pd(PPh₃)₂Cl₂ (84 mg, 0.12 mmol) in DMF (30 mL) was added CuI (23 mg, 0.12 mmol). The mixture was degassed and charged with nitrogen for three times. Then trimethyl silyl acetylene (0.68 mL, 4.84 mmol) and Et₃N (6.75 mL, 48.4 mmol) was added. The mixture was stirred at 70 °C for 2 hours. After the removal of the solvent, the residue was diluted with DCM (200 mL) and washed with water (100 mL x 3). The separated phase was dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a light yellow solid (0.67 g, 84%).

MS (ESI, pos. ion) m/z: 462.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 0.27 (s, 9H), 3.99 (s, 3H), 6.85 (d, *J*=8.6 Hz, 1H), 7.48 (t, *J*=8.0 Hz, 2H), 7.58 (t, *J*=7.4 Hz, 1H), 7.77 (dd, *J*=8.6 Hz, 2.6 Hz, 1H), 7.95 (s, 1H), 7.99 (d, *J*=2.2 Hz, 1H), 8.19 (d, *J*=7.4 Hz, 2H), 8.37 (d, *J*=2.1 Hz, 1H), 8.60 (d, *J*=2.0 Hz, 1H).

Step 5) 3-ethynyl-5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

To a suspension of 5-(6-methoxypyridin-3-yl)-1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridine (0.67 g, 1.45 mmol) in THF (60 mL) was added tetra-*n*-butyl ammonium fluoride (0.76 g, 2.90 mmol). The mixture was stirred at rt for 1.5 hours 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 light yellow solid (0.30 g, 83%).

MS (ESI, pos. ion) m/z: 250.0 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 3.23 (s, 1H), 4.00 (s, 3H), 6.86 (d, *J*=8.6 Hz, 1H), 7.62 (s, 1H), 7.83 (dd, *J*=8.6 Hz, 2.5 Hz, 1H), 8.17 (d, *J*=2.0 Hz, 1H), 8.43 (d, *J*=2.3 Hz, 1H), 8.52 (s, 1H), 9.34 (s, 1H).

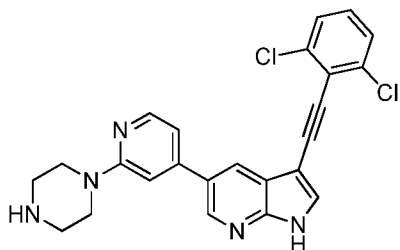
Step 6) 3-((2,6-dichlorophenyl)ethynyl)-5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of 3-ethynyl-5-(6-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (0.10 g, 0.40 mmol), 1,3-dichloro-2-bromobenzene (90 mg, 0.40 mmol), Pd(PPh₃)₂Cl₂ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol), and Et₃N (1.12 mL, 8.02 mmol) in DMF (4 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a white solid (26 mg, 14%).

MS (ESI, pos. ion) m/z: 394.0 (M+1);

^1H NMR (400 MHz, CDCl_3): δ 3.91 (s, 3H), 6.94 (d, $J=8.9$ Hz, 1H), 7.37 (t, $J=8.4$ Hz, 1H), 7.59 (d, $J=8.1$ Hz, 2H), 8.07 (d, $J=2.6$ Hz, 1H), 8.09 (d, $J=2.6$ Hz, 1H), 8.17 (d, $J=2.0$ Hz, 1H), 8.52 (d, $J=2.2$ Hz, 1H), 8.62 (d, $J=1.8$ Hz, 1H), 12.47 (s, 1H).

Example 7 3-((2,6-dichlorophenyl)ethynyl)-5-(2-(piperazin-1-yl)pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine



Step 1) tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate

To a suspension of 2-(1-piperazinyl)pyridine-4-boronic acid pinacol ester (0.55 g, 1.90 mmol) and DMAP (23 mg, 0.19 mmol) in THF (50 mL) was added Et_3N (0.4 mL, 2.85 mmol) and $(\text{Boc})_2\text{O}$ (0.49 mL, 2.28 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 minutes, then warmed up to rt and continued to stirred for a further 4 hours. After the removal of the solvent, the residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 10/1) to give the title compound as a light yellow solid (0.58 g, 78%).

MS (ESI, pos. ion) m/z : 308.2 ($M+1-82$);

^1H NMR (400 MHz, CDCl_3): δ 1.33(s, 12H), 1.48 (s, 9H), 3.54 (s, 8H), 6.96 (d, $J=4.8$ Hz, 1H), 7.04 (s, 1H), 8.20 (d, $J=4.8$ Hz, 1H).

Step 2) tert-butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate (0.37 g, 0.99 mmol), 5-bromo-7-azaindole (0.15 g, 0.76 mmol), $\text{Pd}(\text{dppf})_2\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (60.0 mg, 0.076 mmol), and Cs_2CO_3 (0.74 g, 2.28 mmol) in DMF (10 mL) and H_2O (2 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a light yellow solid (0.25 g, 65%).

MS (ESI, pos. ion) m/z : 380.2 ($M+1$);

¹H NMR (400 MHz, CDCl₃): δ 1.49 (s, 9H), 3.60 (m, 8H), 6.58 (m, 1H), 6.87 (s, 1H), 6.93 (dd, *J*=5.2 Hz, 1.3 Hz, 1H), 7.38 (m, 1H), 8.15 (d, *J*=1.8 Hz, 1H), 8.26 (d, *J*=5.4 Hz, 1H), 8.55 (d, *J*=2.2 Hz, 1H), 9.15 (s, 1H).

Step 3) tert-butyl 4-(4-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate

To a suspension of tert-butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate (1.0 g, 4.44 mmol) in acetone (35 mL) was added NIS (1.2 g, 5.33 mmol). The mixture was stirred at rt for 1.5 hours 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 light yellow solid (0.26 g, 97%).

MS (ESI, pos. ion) *m/z*: 506.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.49 (s, 9H), 3.61 (m, 8H), 6.87 (s, 1H), 6.94 (dd, *J*=4.0 Hz, 1.1 Hz, 1H), 7.50 (d, *J*=2.3 Hz, 1H), 7.93 (d, *J*=1.8 Hz, 1H), 8.28 (d, *J*=5.2 Hz, 1H), 8.55 (d, *J*=2.0 Hz, 1H), 9.54 (s, 1H).

Step 4) tert-butyl 4-(4-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared according to the procedure as described in Example 6 Step 3 by using a mixture of tert-butyl 4-(4-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridine-2-yl)piperazine-1-carboxylate (0.33 g, 0.65 mmol), *n*-Bu₄NHSO₄ (0.022 g, 0.065 mmol), PhSO₂Cl (0.13 mL, 0.98 mmol) and 50% aqueous NaOH (0.13 g, 1.63 mmol) in DCM (30 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (0.40 g, 95%).

MS (ESI, pos. ion) *m/z*: 646.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.49 (s, 9H), 3.59 (d, *J*=5.8 Hz, 8H), 6.78 (s, 1H), 6.84 (d, *J*=5.1 Hz, 1H), 7.49 (m, 2H), 7.62 (t, *J*=7.4 Hz, 1H), 7.80 (d, *J*=2.0 Hz, 1H), 7.91 (s, 1H), 8.22 (d, *J*=7.6 Hz, 2H), 8.26 (d, *J*=5.2 Hz, 1H), 8.64 (d, *J*=1.8 Hz, 1H).

Step 5) tert-butyl 4-(4-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate

To a suspension of tert-butyl 4-(4-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate (0.40 g, 0.62 mmol) in DMF (30 mL) was added Pd(PPh₃)₂Cl₂ (22 mg, 0.03 mmol) and CuI (6 mg, 0.03 mmol). The mixture was degassed and charged with nitrogen for three times. Then trimethyl silyl acetylene (0.17 mL, 1.24 mmol) and

Et₃N (0.86 mL, 6.20 mmol) was added. The mixture was stirred at 75 °C for 2 hours. After the removal of the solvent, the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (0.30 g, 78%).

MS (ESI, pos. ion) m/z: 616.2 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 0.28 (s, 9H), 1.49 (s, 9H), 3.60 (d, *J*=5.4 Hz, 8H), 6.78 (s, 1H), 6.84 (dd, *J*=5.1 Hz, 1.08 Hz, 1H), 7.49 (t, *J*=7.4 Hz, 2H), 7.61 (t, *J*=7.4 Hz, 1H), 7.97 (s, 1H), 8.05 (d, *J*=2.1 Hz, 1H), 8.20 (d, *J*=7.4 Hz, 2H), 8.26 (d, *J*=5.1 Hz, 1H), 8.64 (d, *J*=2.0 Hz, 1H).

Step 6) tert-butyl 4-(4-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate

To a suspension of tert-butyl 4-(4-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate (0.30 g, 0.49 mmol) in THF (10 mL) was added a solution of tetra-*n*-butyl ammonium fluoride (0.97 mL, 0.97 mmol, 1 M in THF). The mixture was stirred at rt for 1.5 hours and concentrated *in vacuo*. The residue was dissolved with DCM (80 mL) and then the mixture was washed with brine (30 mL x 2). The separated organic layer 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 a light yellow solid (0.19 g, 96%).

MS (ESI, pos. ion) m/z: 404.3 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.50 (s, 9H), 3.25 (s, 1H), 3.61 (m, 8H), 6.88 (s, 1H), 6.95 (d, *J*=5.2 Hz, 1H), 7.69 (s, 1H), 8.26 (d, *J*=1.9 Hz, 1H), 8.28 (d, *J*=5.2 Hz, 1H), 8.61 (d, *J*=1.8 Hz, 1H), 11.40 (s, 1H).

Step 7) tert-butyl 4-(4-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 4-(4-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate (0.20 g, 0.49 mmol), 1,3-dichloro-2-bromobenzene (112 mg, 0.49 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.022 mmol), CuI (4 mg, 0.022 mmol), and Et₃N (1.40 mL, 9.92 mmol) in DMF (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a yellow solid (0.17 g, 62%).

MS (ESI, pos. ion) m/z: 548.2 (M+1);

^1H NMR (400 MHz, CDCl_3): δ 1.49 (s, 9H), 3.63 (m, 8H), 6.89 (s, 1H), 6.95 (d, $J=5.2$ Hz, 1H), 7.19 (t, $J=8.4$ Hz, 1H), 7.38 (d, $J=8.1$ Hz, 2H), 7.75 (d, $J=1.9$ Hz, 1H), 8.28 (d, $J=5.2$ Hz, 1H), 8.39 (d, $J=1.8$ Hz, 1H), 8.63 (s, 1H), 9.79 (s, 1H).

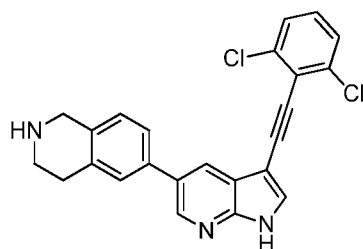
Step 8) 3-((2,6-dichlorophenyl)ethynyl)-5-(2-(piperazin-1-yl)pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine

The titled compound was prepared according to the procedure as described in Example 2 Step 5 by using a mixture of tert-butyl 4-(4-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)piperazine-1-carboxylate (0.17 g, 0.31 mmol), and a solution of HCl in EtOAc (3.10 mL, 12.4 mmol, 4 M) in DCM (10 mL). The crude product was recrystallized by DCM (8 mL) to give the title compound as a gray solid (47 mg, 33%).

MS (ESI, pos. ion) m/z : 448.1 ($M+1$);

^1H NMR (400 MHz, CDCl_3): δ 3.03 (m, 4H), 3.61 (m, 4H), 6.93 (s, 1H), 6.97 (d, $J=5.2$ Hz, 1H), 7.20 (t, $J=8.1$ Hz, 1H), 7.39 (d, $J=8.1$ Hz, 2H), 7.76 (s, 1H), 8.24 (d, $J=5.2$ Hz, 1H), 8.40 (d, $J=2.0$ Hz, 1H), 8.55 (d, $J=1.9$ Hz, 1H).

Example 8 6-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1,2,3,4-tetrahydroisoquinoline



Step 1) tert-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 7 Step 1 by using a mixture of 6-bromo-1,2,3,4-tetrahydroisoquinoline (1.00 g, 4.72 mmol), $(\text{Boc})_2\text{O}$ (1.21 mL, 5.66 mmol), DMAP (58 mg, 0.47 mmol) and Et_3N (1.00 mL, 7.07 mmol) in THF (45 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 20/1) to give the title compound as a colourless sticky liquid (1.38 g, 93%).

MS (ESI, pos. ion) m/z : 256.0 ($M+1-56$);

^1H NMR (400 MHz, CDCl_3): δ 1.48 (s, 9H), 2.80 (t, $J=5.4$ Hz, 2H), 3.61 (m, 2H), 4.50 (s, 2H), 6.97 (d, $J=8.0$ Hz, 1H), 7.29 (d, $J=7.4$ Hz, 2H).

Step 2) tert-butyl 6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of 7-azaindole-5-boronic acid pinacol ester (1.40 g, 5.75 mmol), tert-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.38 g, 4.42 mmol), Pd(dppf)₂Cl₂·CH₂Cl₂ (0.36 g, 0.44 mmol) and Cs₂CO₃ (4.32 g, 13.26 mmol) in DMF (20 mL) and H₂O (4 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/2) to give the title compound as a light yellow solid (1.35 g, 87%).

MS (ESI, pos. ion) m/z: 350.2 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.51 (s, 9H), 2.93 (m, 2H), 3.70 (m, 2H), 4.64 (s, 2H), 6.56 (m, 1H), 7.22 (d, *J*=7.9 Hz, 1H), 7.40 (m, 2H), 7.46 (d, *J*=7.8 Hz, 1H), 8.11 (d, *J*=1.6 Hz, 1H), 8.54 (d, *J*=1.9 Hz, 1H), 9.84 (s, 1H).

Step 3) tert-butyl 6-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a suspension of tert-butyl 6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.50 g, 1.43 mmol) in acetone (10 mL) was added NIS (0.39 g, 1.72 mmol). The mixture was stirred at rt for 1.5 hours, then filtered and the filter cake was washed with cooled acetone (6 mL). The filtrate was concentrated *in vacuo*. The residue and the filter cakes were purified together by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a light yellow solid (0.61 g, 97%).

MS (ESI, pos. ion) m/z: 476.1 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.51 (s, 9H), 2.94 (m, 2H), 3.71 (m, 2H), 4.65 (s, 2H), 7.23 (m, 1H), 7.43 (m, 1H), 7.48 (d, *J*=9.2 Hz, 2H), 7.90 (d, *J*=1.8 Hz, 1H), 8.55 (d, *J*=1.6 Hz, 1H), 10.43 (s, 1H).

Step 4) tert-butyl 6-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 6 Step 3 by using a mixture of tert-butyl 6-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.61 g, 1.28 mmol), *n*-Bu₄NHSO₄ (0.044 g, 0.128 mmol), PhSO₂Cl (0.25 mL, 1.93 mmol), and 50% aqueous NaOH (0.26 g, 3.21 mmol) in DCM (15 mL) was stirred at rt for 2 hours. The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (0.70 g, 88%).

MS (ESI, pos. ion) m/z: 616.0 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.50 (s, 9H), 2.91 (t, *J*=5.2 Hz, 2H), 3.69 (m, 2H), 4.62 (s, 2H), 7.22 (d, *J*=7.3 Hz, 1H), 7.34 (s, 1H), 7.39 (d, *J*=7.9 Hz, 1H), 7.51 (t, *J*=7.4 Hz, 2H), 7.61 (t, *J*=7.4 Hz, 1H), 7.77 (d, *J*=2.0 Hz, 1H), 7.89 (s, 1H), 8.23 (m, 2H), 8.62 (d, *J*=2.0 Hz, 1H).

Step 5) tert-butyl 6-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 6-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.54 g, 0.88 mmol), trimethyl silyl acetylene (0.25 mL, 1.75 mmol), Pd(PPh₃)₂Cl₂ (31 mg, 0.044 mmol), CuI (8 mg, 0.044 mmol) and Et₃N (2.45 mL, 17.55 mmol) in DMF (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (0.46 g, 89%).

MS (ESI, pos. ion) *m/z*: 586.3 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 0.28 (s, 9H), 1.50 (s, 9H), 2.91 (m, 2H), 3.69 (m, 2H), 4.62 (s, 2H), 7.22 (d, *J*=7.9 Hz, 1H), 7.34 (s, 1H), 7.39 (d, *J*=8.1 Hz, 1H), 7.51 (t, *J*=7.9 Hz, 2H), 7.61 (t, *J*=7.4 Hz, 1H), 7.94 (s, 1H), 8.01 (d, *J*=2.1 Hz, 1H), 8.21 (m, 2H), 8.63 (d, *J*=2.0 Hz, 1H).

Step 6) tert-butyl 6-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 7 Step 6 by using a mixture of tert-butyl 6-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.58 g, 0.99 mmol), and a solution of tetra-*n*-butyl ammonium fluoride (2.0 mL, 2.0 mmol, 1 M in THF) in THF (10 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a brown yellow solid (0.27 g, 73%).

MS (ESI, pos. ion) *m/z*: 374.2 (M+1);

¹H NMR (400 MHz, CDCl₃): δ 1.51 (s, 9H), 2.94 (m, 2H), 3.23 (s, 1H), 3.71 (m, 2H), 4.65 (s, 2H), 7.23 (d, *J*=8.0 Hz, 1H), 7.44 (s, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 7.65 (d, *J*=1.5 Hz, 1H), 8.22 (d, *J*=1.9 Hz, 1H), 8.59 (d, *J*=1.9 Hz, 1H), 10.81 (s, 1H).

Step 7) tert-butyl 6-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 6-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-

dihydroisoquinoline-2(1H)-carboxylate (0.15 g, 0.40 mmol), 1,3-dichloro-2-bromobenzene (91 mg, 0.40 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol), and Et_3N (1.12 mL, 8.03 mmol) in DMF (3 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (0.08 g, 38%).

MS (ESI, pos. ion) m/z : 518.2 ($M+1$);

^1H NMR (400 MHz, CDCl_3): δ 1.51 (s, 9H), 2.95 (m, 2H), 3.71 (m, 2H), 4.65 (s, 2H), 7.17 (t, $J=8.1$ Hz, 1H), 7.24 (m, 1H), 7.37 (d, $J=8.1$ Hz, 2H), 7.44 (s, 1H), 7.49 (d, $J=8.1$ Hz, 1H), 7.75 (d, $J=1.6$ Hz, 1H), 8.35 (d, $J=1.8$ Hz, 1H), 8.61 (m, 1H), 10.52 (s, 1H).

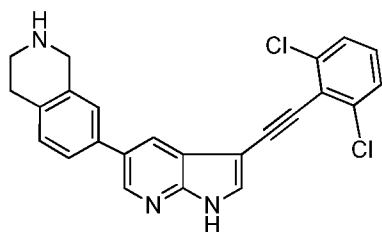
Step 8) 6-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1,2,3,4-tetrahydroisoquinoline

The titled compound was prepared according to the procedure as described in Example 2 Step 5 by using a mixture of tert-butyl 6-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.08 g, 0.15 mmol), and a solution of HCl in EtOAc (1.54 mL, 6.16 mmol, 4 M) in DCM (5 mL). The crude product was recrystallized by DCM (6 mL) to give the title compound as a light yellow solid (40 mg, 62%).

MS (ESI, pos. ion) m/z : 418.1 ($M+1$);

^1H NMR (400 MHz, CDCl_3): δ 2.80 (m, 2H), 3.00 (m, 2H), 3.91 (s, 2H), 7.15 (d, $J=8.1$ Hz, 1H), 7.41 (m, 3H), 7.60 (d, $J=8.1$ Hz, 2H), 8.08 (s, 1H), 8.17 (d, $J=2.1$ Hz, 1H), 8.60 (d, $J=2.1$ Hz, 1H), 12.40 (s, 1H).

Example 9 7-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1,2,3,4-tetrahydroisoquinoline



Step 1) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine

To a solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (19.7 g, 100 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (30.5 g, 120 mmol) in 1,4-dioxane (400 mL) was added CH_3COOK (19.6 g, 200 mmol). The mixture was degassed and charged with nitrogen for three times. Then $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (1.6 g, 2 mmol) was added. The mixture was stirred at 80 °C

under nitrogen atmosphere for overnight, then cooled to rt, and concentrated *in vacuo*. The residue was diluted with EtOAc (500 mL) and washed with brine (300 mL x 3). 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 crude product, then the crude product was then recrystallized by PE/EtOAc (10/1 (v/v), 25 mL) to give the title compound as a white solid (23.4 g, 95.9%).

MS (ESI, pos. ion) m/z: 245.2 (M+1);

¹HNMR (400MHz, DMSO-*d*₆): δ 1.31 (s, 12H), 6.48 (d, *J*=3.4 Hz, 1H), 7.47 (d, *J*=3.1 Hz, 1H), 8.22 (d, *J*=1.4 Hz, 1H), 8.44 (d, *J*=1.4 Hz, 1H), 11.75 (s, 1H).

Step 2) tert-butyl 7-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 7-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.32 g, 4.2 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (1.14 g, 4.65 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (0.35g, 0.42mmol) and Cs₂CO₃ (4.12 g, 12.7 mmol) in DMF/H₂O (5/1, 12 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/2) to give the title compound as a brown liquid (1.68 g, 100%).

MS (ESI, pos. ion) m/z: 350.2 (M+1).

Step 3) tert-butyl 7-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of tert-butyl 7-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.68 g, 4.8 mmol) in acetone (50 mL) was added NIS (1.30 g, 5.77 mmol). The mixture was stirred at rt for 2 hours. After the removal of the solvent partly, the precipitate was collected by filtration and washed with ice-cold acetone. Then the filtrate was concentrated. The residue and the precipitate were purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a brown solid (1.98 g, 86.7%).

MS (ESI, pos. ion) m/z: 476.1 (M+1).

Step 4) tert-butyl 7-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 6 Step 3 by using a mixture of tert-butyl 7-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.98 g, 4.17 mmol), PhSO₂Cl (0.81 mL, 6.25 mmol), *n*-Bu₄NHSO₄ (0.142 g, 0.42 mmol) and 50% aqueous NaOH solution (0.42 g, 10.43 mmol) in

DCM (60 mL) was stirred at rt for 2 hours. The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (0.78 g, 30.4%).

MS (ESI, pos. ion) m/z: 616.0 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 1.43 (s, 9H), 2.81 (s, 2H), 4.02 (s, 2H), 4.58 (s, 2H), 7.26-7.28 (d, *J*=8.2 Hz, 1H), 7.55-7.57 (d, *J*=8.1 Hz, 1H), 7.61-7.62 (d, *J*=4.3 Hz, 1H), 7.64-7.66 (d, *J*=8.5 Hz, 2H), 7.73-7.74 (d, *J*=4.1 Hz, 1H), 7.92-7.93 (d, *J*=4.0 Hz, 1H), 8.15-8.17 (d, *J*=8.3 Hz, 2H), 8.22 (s, 1H), 8.69-8.70 (d, *J*=4.6 Hz, 1H).

Step 5) tert-butyl 7-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 7-(3-iodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.78 g, 1.27 mmol), trimethyl silyl acetylene (0.187 g, 1.90 mmol), Pd(PPh₃)₂Cl₂ (88.9 mg, 0.13 mmol), CuI (24.13 mg, 0.13 mmol), and Et₃N (2.5 g, 25.3 mmol) in DMF (15 mL). The crude product was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a light yellow solid (0.68 g, 91.6%).

MS (ESI, pos. ion) m/z: 586.3 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 0.27 (s, 9H), 1.43 (s, 9H), 2.81 (s, 2H), 4.02 (s, 2H), 4.58 (s, 2H), 7.26-7.28 (d, *J*=8.2 Hz, 1H), 7.55-7.57 (d, *J*=8.0 Hz, 1H), 7.61-7.62 (d, *J*=4.1 Hz, 1H), 7.63-7.65 (d, *J*=8.4 Hz, 2H), 7.75-7.77 (d, *J*=8.3 Hz, 1H), 8.10-8.11 (d, *J*=4.2 Hz, 1H), 8.15-8.17 (d, *J*=8.3 Hz, 2H), 8.32 (s, 1H), 8.71-8.72 (d, *J*=4.6 Hz, 1H).

Step 6) tert-butyl 7-(3-ethynyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a suspension of tert-butyl 7-(1-(phenylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.68 g, 1.16 mmol) in THF (20 mL) was added tetra-*n*-butyl ammonium fluoride (0.61 g, 2.32 mmol). The mixture was stirred at rt for 2 hours, concentrated *in vacuo* and the residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a light yellow solid (0.31g, 71.5%).

MS (ESI, pos. ion) m/z: 374.2 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 1.44 (s, 9H), 2.80-2.83 (m, 2H), 3.57-3.59 (m, 2H), 4.15 (s, 1H), 4.46-4.60 (m, 2H), 7.25-7.27 (d, *J*=8.1 Hz, 1H), 7.54-7.56 (d, *J*=8.2 Hz, 1H), 7.59 (s, 1H), 7.89-7.90 (d, *J*=4.2 Hz, 1H), 8.13-8.14 (d, *J*=4.2 Hz, 1H), 8.58-8.59 (d, *J*=4.6 Hz, 1H), 12.15 (s, 1H).

Step 7) tert-butyl 7-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

The titled compound was prepared according to the procedure as described in Example 3 Step 1 by using a mixture of tert-butyl 7-(3-ethynyl-1H-pyrrolo[2,3-b]pyridine-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.31 g, 0.83 mmol), 1,3-dichloro-2-bromobenzene (0.19 g, 0.83 mmol), Pd(PPh₃)₂Cl₂ (29 mg, 0.04 mmol), CuI (7.9 mg, 0.04 mmol), and Et₃N (1.83 g, 16.6 mmol) in DMF (15 mL). The crude product was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a light yellow solid (0.15 g, 36.5%).

MS (ESI, pos. ion) *m/z*: 518.2 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 1.44 (s, 9H), 2.81-2.84 (m, 2H), 3.57-3.60 (m, 2H), 4.55-4.60 (m, 2H), 7.28-7.20 (d, *J*=8.2 Hz, 1H), 7.37-7.42 (m, 1H), 7.51-7.56 (m, 2H), 7.59-7.61 (d, *J*=8.2 Hz, 2H), 7.95 (s, 1H), 8.08-8.09 (d, *J*=4 Hz, 1H), 8.19-8.20 (d, *J*=4.1 Hz, 1H), 8.63-8.64 (d, *J*=4.5 Hz, 1H), 12.43 (s, 1H).

Step 8) 7-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1,2,3,4-tetrahydroisoquinoline

The titled compound was prepared according to the procedure as described in Example 2 Step 5 by using a mixture of tert-butyl 7-(3-((2,6-dichlorophenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.15 g, 0.3 mmol), and a solution of HCl in EtOAc (4 mL, 16.0 mmol, 4 M) in DCM (15 mL). The crude product was recrystallized by DCM (8 mL) to give the title compound as a light yellow solid (110 mg, 90.9%).

MS (ESI, pos. ion) *m/z*: 418.1 (M+1);

¹H NMR (400 MHz, DMSO-*d*₆): δ 2.70-2.73 (m, 2H), 2.95-2.98 (m, 2H), 3.92 (m, 2H), 7.17-7.19 (d, *J*=8.3 Hz, 1H), 7.36-7.37 (d, *J*=4.0 Hz, 1H), 7.39-7.44 (m, 2H), 7.59-7.61 (d, *J*=8.2 Hz, 2H), 8.07 (s, 1H), 8.16-8.17 (d, *J*=4.2 Hz, 1H), 8.59-8.60 (d, *J*=4.6 Hz, 1H), 12.30 (s, 1H).

BIOLOGICAL TESTING

The LC/MS/MS system used in the analysis consists of an Agilent 1200 Series vacuum degasser, binary pump, well-plate autosampler, thermostatted column compartment, the Agilent G6430

Triple Quadrupole Mass Spectrometer with an electrospray ionization (ESI) source. Quantitative analysis was carried out using MRM mode. The parameters for MRM transitions are in the Table A.

Table A

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

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

Table B

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

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

injected.

Example A: Compound Stability In Human And Rat Liver Microsomes

Human or rat liver microsomes incubations were conducted in duplicate in polypropylene tubes. The typical incubation mixtures consisted of human liver microsomes (0.5 mg protein/mL), compounds of interest (5 μ M) and NADPH (1.0 mM) in a total volume of 200 μ L potassium phosphate buffer (PBS, 100 mM, pH7.4). Compounds were dissolved in DMSO and diluted with PBS such that the final concentration of DMSO was 0.05%. The enzymatic reactions were commenced with the addition of protein after a 3-min preincubation and incubated in a water bath open to the air at 37 °C. Reactions were terminated at various time points (0, 5, 10, 15, 30, 60 min) by adding equal volume of ice-cold acetonitrile. The samples were stored at -80 °C until LC/MS/MS assays.

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

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

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

Data Analysis

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

Table 2 Human and rat liver microsomes Stability

Example #	Human		Rat	
	T _{1/2} (min)	CL _{int} (mL/min/kg)	T _{1/2} (min)	CL _{int} (mL/min/kg)

Ex. 1	418.7	4.2	716.1	3.5
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The compounds disclosed herein exhibited desirable half-life ($T_{1/2}$) when the compounds were incubated in human and rat liver microsomes.

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

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

Example C: Kinase Assays

Kinase assays can be performed by measurement of incorporation of γ - ^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) are coated with MBP (Sigma #M-1891) by incubation of 60 μL /well of 20 $\mu\text{g/mL}$ 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 MgCl_2 , 1 mM DTT, 0.02% TritonX-100). Compound dilutions are performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point is measured in duplicate, and at least two duplicate assays are performed for each individual compound determination. Enzyme is added to final concentrations of 10 nM or 20 nM, for example. A mixture of unlabeled ATP and γ - ^{33}P ATP is added to start the reaction (2 x 10^6 cpm of γ - ^{33}P ATP per well (3000 Ci/mmol) and 10 μM unlabeled ATP, typically. The reactions are carried out for 1 h at rt with shaking. Plates are washed 7x with TBS, followed by the addition of 50 μL /well scintillation fluid (Wallac). Plates are read using a Wallac Trilux counter. This is only one format of such assays; various other formats are possible, as known to one skilled in the art.

The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition

constant, K_i . The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the condition of the assay. The IC_{50} value is estimated by preparing a 10 point curve using a $\frac{1}{2}$ 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).

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

ALK (h) Kinase Assay

ALK (h) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μ M KKKSPGEYVNIEFG, 10 mM MgAcetate and [γ - 33 P-ATP] (specific activity approx. 500 pcm/pmol, concentration as required (10 μ M)). The reaction is initiated by the addition of the MgATP 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 filter mat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

c-Met (h) Kinase Assay

Met (h) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μ M KKKSPGEYVNIEFG, 10 mM MgAcetate and [γ - 33 P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required (10 μ M)). The reaction is initiated by the addition of the MgATP 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.

Table 3 Kinase inhibition data

Example #	IC ₅₀ (nM)	
	ALK	Met
Ex. 1	58	/
Ex. 5	985	/
Ex. 7	392	/
Ex. 8	91	93
Ex. 9	155	/

The compounds disclosed herein exhibited potent activities in the ALK and c-Met (h) assays.

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

For most assays, kinase-tagged T7 phage strains were prepared in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage and incubated with shaking at 32 °C until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SEABLOCK™ (Pierce), 1% BSA, 0.05% TWEEN®20, 1 mM DTT) to remove unbound ligand and to reduce nonspecific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SEABLOCK™, 0.17x PBS, 0.05% TWEEN®20, 6 mM DTT). All reactions were performed in polystyrene 96-well plates in a final volume of 0.135 mL. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% TWEEN®20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% TWEEN®20, 0.5 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

The kinase assays described herein were performed using KINOMEscan™ Profiling Service at DiscoveRx Corporation, 42501 Albrae St. Fremont, CA 94538, USA.

Example D: Tumor Xenograft Models

The efficacy of compounds disclosed herein is evaluated in a standard murine model of tumorigenesis. Human tumor cells (such as U87MG glioblastoma cells, MKN45 Gastric Adenocarcinoma cells, MDA-MB-231 breast adenocarcinoma cells, or Caki-1 renal carcinoma cells, all from ATCC) are expended in culture, harvested, and injected subcutaneously onto the rear flank of 6-7 week old female athymic nude mice (BALB/cA nu/nu, Shanghai SLAC Laboratory Animal, Co.) (n = 10 for vehicle group, n = 8 for each dosing group). When tumors reaches a volume of 100-250 mm³, animals are randomly divided into vehicle control (for

example, 2% HPMC + 1% Tween-80 in water) and compound groups. Subsequent administration of compound by oral gavage (for example, 3-50 mpk/dose, dissolved in 2% HPMC + 1% Tween-80 in water) begins anywhere from day 0 to day 15 post tumor cell challenge and generally continues with once a day for the duration of the experiment.

Tumor Growth Inhibition (TGI) Analysis

Progression of tumor growth is assessed by tumor volumes and recorded as a function of time. The long (L) and short (W) axes of the subcutaneous tumors are measured with calipers twice weekly, and the tumor volume (TV) calculated as $(L \times W^2)/2$. TGI is calculated from the difference between the median tumor volumes of vehicle-treated and drug-treated mice, expressed as a percentage of the median tumor volume of the vehicle-treated control group, by the following relation:

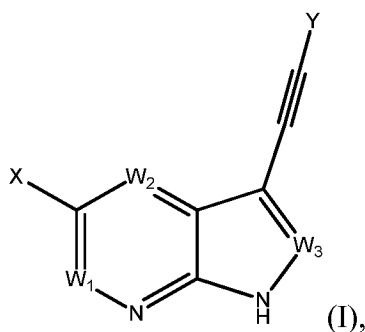
$$\%TGI = \left(\frac{\text{Median Tumor Volume}_{\text{control}} - \text{Median Tumor Volume}_{\text{drug-treated}}}{\text{Median Tumor Volume}_{\text{control}}} \right) \times 100$$

Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), Followed by Scheffe psot hoc testing for multiple comparisons. Vehicle alone (2% HPMC + 1% Tween-80, or the like) is the negative control.

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:

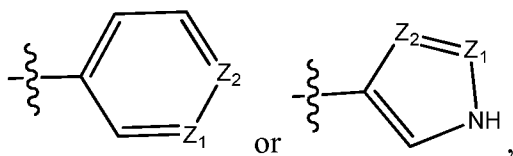
1. A compound having Formula (I):



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

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

X is



wherein each of Z_1 and Z_2 is independently N, or CH, and X is optionally substituted by one, two, or three R^1 groups;

each R^1 is independently D, F, Cl, Br, I, CN, NO_2 , N_3 , OR^a , SR^a , NR^aR^b , (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, $-(C_1-C_4)$ alkylene-CN, $-(C_1-C_4)$ alkylene- NR^aR^b , $-(C_1-C_4)$ alkylene- OR^a , (C_3-C_{10}) cycloalkyl, $-(C_1-C_4)$ alkylene- (C_3-C_{10}) cycloalkyl, (C_3-C_{10}) heterocyclyl, $-(C_1-C_4)$ alkylene- (C_3-C_{10}) heterocyclyl, (C_6-C_{10}) aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, $-(C_1-C_4)$ alkylene- (C_6-C_{10}) aryl, or $-(C_1-C_4)$ alkylene-(5-10 membered heteroaryl), provided that when each of Z_1 and Z_2 is CH, R^1 is not OR^a or NR^aR^b ;

each hydrogen in R^1 is optionally substituted by R^2 , and R^1 groups on adjacent atoms may combine to form a (C_4-C_{10}) cycloalkyl or (C_3-C_{10}) heterocyclyl, wherein each of the (C_4-C_{10}) cycloalkyl and (C_3-C_{10}) heterocyclyl is optionally substituted by one, two, three, or four R^2 groups;

each R^2 is independently D, F, Cl, Br, I, CN, NO₂, N₃, OR^a, SR^a, NR^aR^b, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-NR^aR^b, -(C₁-C₄)alkylene-OR^a, (C₃-C₈)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, (C₃-C₈)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₈)heterocyclyl;

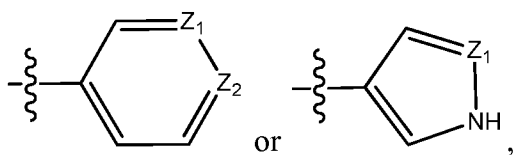
Y is (C₆-C₁₀)aryl, or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the (C₆-C₁₀)aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, I, CN, NO₂, N₃, OR^a, SR^a, S(=O)R^a, S(=O)₂R^a, NR^aR^b, S(=O)₂NR^aR^b, OC(=O)R^a, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₁-C₄)alkylene-CN, -(C₁-C₄)alkylene-OR^a, (C₃-C₈)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, (C₃-C₈)heterocyclyl and -(C₁-C₄)alkylene-(C₃-C₈)heterocyclyl;

each R^a and R^b is independently H, (C₁-C₆)aliphatic, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₆)cycloalkyl, (C₃-C₆)heterocyclyl, or -(C₁-C₄)alkylene-(C₃-C₆)heterocyclyl, wherein each of the (C₁-C₆)aliphatic, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkylene-(C₃-C₆)cycloalkyl, (C₃-C₆)heterocyclyl and -(C₁-C₄)alkylene-(C₃-C₆)heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, OH, NH₂, (C₁-C₆)alkoxy and (C₁-C₆)alkylamino;

each R^c is independently H, D, F, Cl, Br, I, N₃, CN, NH₂, NHS(=O)₂(C₁-C₆)alkyl, N(R^a)C(=O)(C₁-C₆)alkyl, NHC(=O)NR^aR^b, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino, (C₃-C₆)cycloalkyl, (C₃-C₆)heterocyclyl, (C₆-C₁₀)aryl, or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino, (C₃-C₆)cycloalkyl, (C₃-C₆)heterocyclyl, (C₆-C₁₀)aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, OH, NH₂, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy and (C₁-C₆)alkylamino.

2. The compound of claim 1, wherein each of W₁ and W₂ is CR^c; W₃ is N or CR^c.

3. The compound of claim 1, wherein X is



wherein each of Z_1 and Z_2 is independently N, or CH; and X is optionally substituted by one, two, or three R^1 groups; R^1 groups on adjacent atoms may combine to form a (C₄-C₁₀)cycloalkyl or (C₃-C₁₀)heterocyclyl.

4. The compound of claim 1, wherein each R^1 is independently D, F, Cl, OR^a, NR^aR^b, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₂-C₄)alkenyl, -(C₁-C₂)alkylene-NR^aR^b, -(C₁-C₂)alkylene-OR^a, (C₃-C₆)cycloalkyl, -(C₁-C₂)alkylene-(C₃-C₆)cycloalkyl, (C₃-C₆)heterocyclyl, or -(C₁-C₂)alkylene-(C₃-C₆)heterocyclyl, with the proviso wherein each of Z_1 and Z_2 is CH, each R^1 is not OR^a or NR^aR^b;

each hydrogen in R^1 is optionally substituted by R^2 , and R^1 groups on adjacent atoms may combine to form a (C₅-C₆)cycloalkyl or (C₃-C₆)heterocyclyl, wherein each of the (C₅-C₆)cycloalkyl and (C₃-C₆)heterocyclyl is optionally substituted by one, two, three, or four R^2 groups.

5. The compound of claim 1, wherein each R^2 is independently D, F, Cl, OR^a, NR^aR^b, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₂-C₆)alkenyl, -(C₁-C₂)alkylene-NR^aR^b, -(C₁-C₂)alkylene-OR^a, (C₃-C₆)cycloalkyl, -(C₁-C₂)alkylene-(C₃-C₆)cycloalkyl, (C₃-C₆)heterocyclyl, or -(C₁-C₂)alkylene-(C₃-C₆)heterocyclyl.

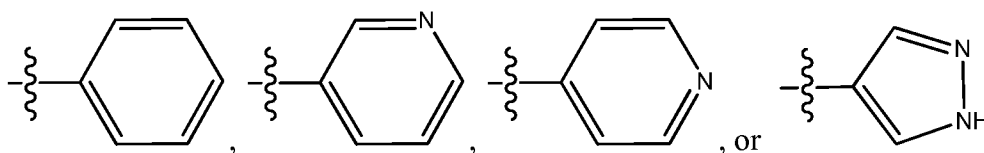
6. The compound of claim 1, wherein Y is a phenyl group optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl and (C₂-C₆)alkynyl.

7. The compound of claim 1, wherein each of R^a and R^b is independently H, (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)heterocyclyl, wherein each of the (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl and (C₃-C₆)heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, N₃, OH, NH₂, (C₁-C₃)alkoxy and (C₁-C₃)alkylamino.

8. The compound of claim 1, wherein each R^c is independently H, D, F, Cl, Br, I, N₃, CN, NH₂, NH(S=O)₂(C₁-C₃)alkyl, N(R^a)C(=O)(C₁-C₃)alkyl, NHC(=O)NR^aR^b, (C₁-

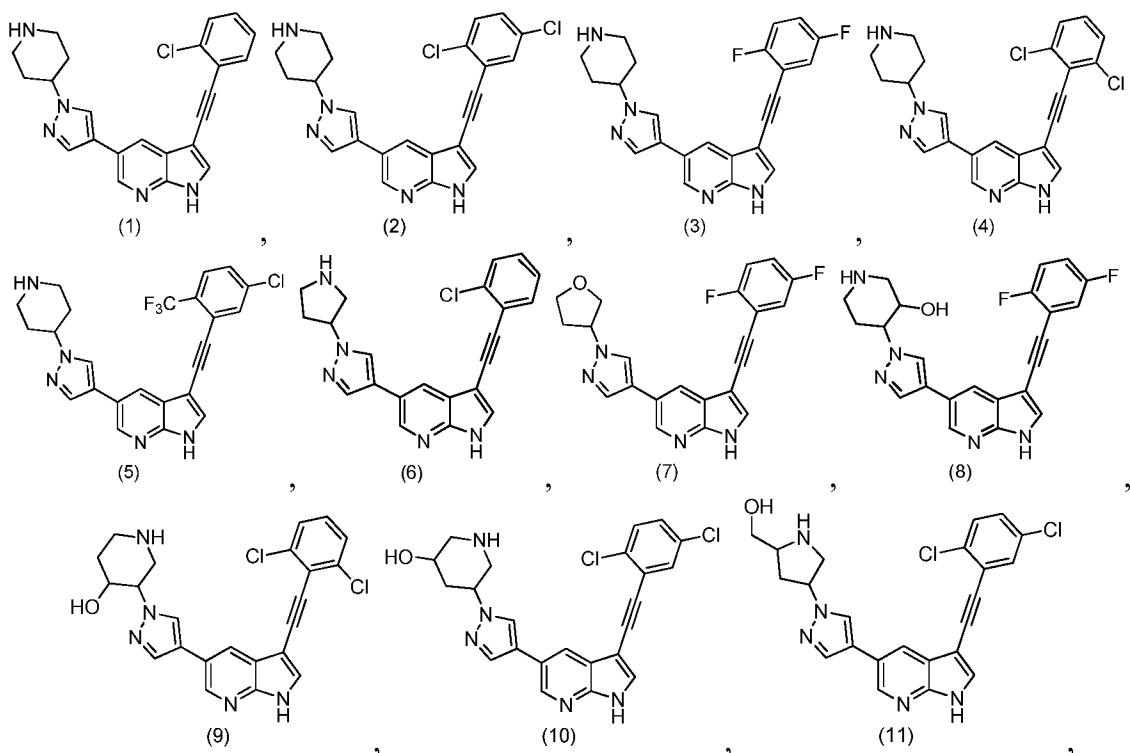
C₃)alkyl, (C₁-C₃)alkoxy, (C₁-C₃)alkylamino, (C₃-C₆)cycloalkyl, or (C₃-C₆)heterocyclyl, wherein each of the (C₁-C₃)alkyl, (C₁-C₃)alkoxy, (C₁-C₃)alkylamino, (C₃-C₆)cycloalkyl and (C₃-C₆)heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N₃, OH, NH₂, (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₃)haloalkyl, (C₁-C₃)alkoxy and (C₁-C₃)alkylamino.

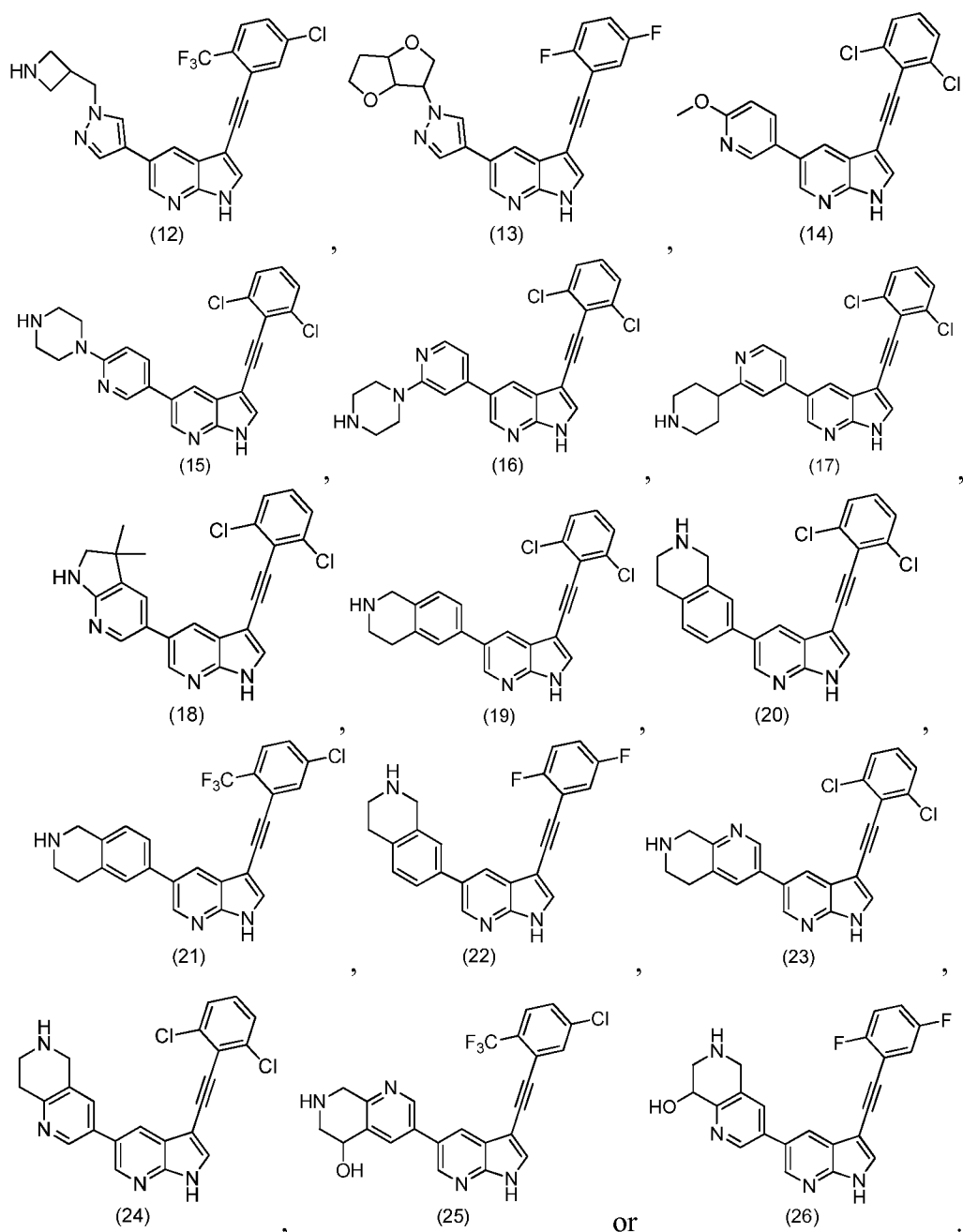
9. The compound of claim 1, wherein X is



Wherein X is optionally substituted by one, two, or three R¹ groups, and each hydrogen in R¹ is optionally substituted by R²; R¹ groups on adjacent atoms may combine to form a (C₄-C₆)heterocyclyl, wherein the (C₄-C₆)heterocyclyl is optionally substituted by one, two, three, or four R² groups.

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





11. A pharmaceutical composition comprising the compound according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

12. The pharmaceutical composition of claim 11 further comprising a therapeutic agent which comprising a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis or a combination thereof.

13. The pharmaceutical composition of claim 12, wherein the therapeutic agent is

adriamycin, rapamycin, temsirolimus, everolimus, ixabepilone, gemcitabin, cyclophosphamide, dexamethasone, etoposide, fluorouracil, afatinib, alisertib, amuvatinib, axitinib, bosutinib, brivanib, cabozantinib, cediranib, crenolanib, crizotinib, dabrafenib, dacomitinib, dasatinib, danusertib, dovitinib, erlotinib, foretinib, ganetespib, gefitinib, ibrutinib, imatinib, iniparib, lapatinib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, niraparib, nilotinib, 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, an interferon, carboplatin, topotecan, taxol, vinblastine, vincristine, temozolomide, tositumomab, trabectedin, belimumab, bevacizumab, brentuximab, cetuximab, gemtuzumab, ipilimumab, ofatumumab, panitumumab, ranibizumab, rituximab, tositumomab, trastuzumab or a combination thereof.

14. The compound according to any one of claims 1 to 10 or the pharmaceutical composition according to any one of claims 11 to 13 for use in preventing, managing, treating or lessening the severity of a proliferative disorder in a patient.

15. The compound or pharmaceutical composition for use of claim 14, 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. Use of the compound according to any one of claims 1 to 10 or the pharmaceutical composition according to any one of claims 11 to 13 in the manufacture of a medicament for preventing, managing, treating or lessening the severity of a proliferative disorder in a patient.

17. The use of claim 16, 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.

18. A method of preventing, managing, treating or lessening the severity of a proliferative disorder in a patient comprising administering to the patient with the compound according to any one of claims 1 to 10 or the pharmaceutical composition according to any one of claims 11 to 13.

19. The method of claim 18, 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.

20. A method of inhibiting or modulating the activity of a protein kinase in a biological sample comprising contacting a biological sample with the compound according to any one of claims 1 to 10 or the pharmaceutical composition according to any one of claims 11 to 13.

21. The method of claim 20, wherein the protein kinase is receptor tyrosine kinase.

22. The method of claim 21, wherein the receptor tyrosine kinase is ALK, c-Met, or a combination thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/73286

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/437 (2014.01)

USPC - 514/300

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): A61K 31/437 (2014.01)

USPC: 514/300

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

USPC: 514/299; 546/112; 546/113

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

PatBase, Google Scholar, SureChem, PubWEST

azaindole, pyrrolo[2,3-b]pyridine, alkyne, acetylene; kinase inhibitor, ALK, cMet, crizotinib

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0142366 A1 (GRACZYK et al.) 21 June 2007 (21.06.2007) para [0051], [0147]-[0148], [0230]	1-13
Y	US 2011/0224191 A1 (CHEN et al.) 15 September 2011 (15.09.2011) para [0183], [0201]-[0202], [0204], [0300], [0307]	1-13
Y	US 2010/0311743 A1 (FARMER et al.) 09 December 2010 (09.12.2010) para [0079]-[0081], [0083], [0114], [0118], [0122]	13

☐ 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

07 March 2014 (07.03.2014)

Date of mailing of the international search report

08 APR 2014

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/73286

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.: 14-22
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.