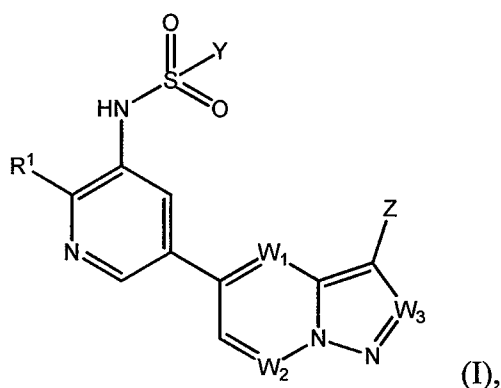


control.

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

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



or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a solvate, a metabolite, a pharmaceutically salt or a prodrug thereof, wherein each of Y, R<sup>1</sup>, Z, W<sub>1</sub>, W<sub>2</sub> and W<sub>3</sub> is as defined herein.

[013] In certain embodiments, each of W<sub>1</sub>, W<sub>2</sub> and W<sub>3</sub> is independently N or CR<sup>c</sup>;

Z is D, CN, N<sub>3</sub>, or  $\text{---}\text{X}$ ;

X is H, D, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, (C<sub>6</sub>-C<sub>10</sub>)aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N<sub>3</sub>, OR<sup>a</sup>, SR<sup>a</sup>, NR<sup>a</sup>R<sup>b</sup>, -C(=O)NR<sup>a</sup>R<sup>b</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)haloalkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-CN, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-OR<sup>a</sup>, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-NR<sup>a</sup>R<sup>b</sup>, (C<sub>6</sub>-C<sub>10</sub>)aryl, and 5-10 membered heteroaryl;

Y is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl,

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.

[036] 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, 75<sup>th</sup> Ed. 1994. Additionally, general principles of organic chemistry are described in Sorrell et al., "Organic Chemistry", University Science Books, Sausalito: 1999, and Smith et al., "March's Advanced Organic Chemistry", John Wiley & Sons, New York: 2007, all of which are incorporated by reference in their entireties.

[037] The grammatical articles "a", "an" and "the", as used herein, are intended to include "at least one" or "one or more" unless otherwise indicated herein or clearly contradicted by the context. Thus, the articles are used herein to refer to one or more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example, "a component" means one or more components, and thus, possibly, more than one component is contemplated and may be employed or used in an implementation of the described embodiments.

[038] 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.

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

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

[041] "Stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include enantiomer, diastereomers, conformer (rotamer), geometric (*cis/trans*) isomer, atropisomer, etc.

[042] "Chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable

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. In some embodiments, the alkenyl group contains 2-8 carbon atoms. In other embodiments, the alkenyl group contains 2-6 carbon atoms. In still other embodiments, the alkenyl group contains 2-4 carbon atoms. Some non-limiting examples of the alkenyl group include ethylenyl or vinyl ( $-CH=CH_2$ ), allyl ( $-CH_2CH=CH_2$ ), and the like.

[060] The term "alkynyl" refers to a 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,  $sp$  triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. In some embodiments, the alkynyl group contains 2-8 carbon atoms. In other embodiments, the alkynyl group contains 2-6 carbon atoms. In still other embodiments, the alkynyl group contains 2-4 carbon atoms. Some non-limiting examples of the alkynyl group include ethynyl ( $-C\equiv CH$ ), propynyl (propargyl,  $-CH_2C\equiv CH$ ),  $-C\equiv C-CH_3$ , and the like.

[061] The term "aliphatic" or "aliphatic group" 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, the aliphatic group contains 1-20 carbon atoms. In some embodiments, the aliphatic group contains 1-10 carbon atoms. In other embodiments, the aliphatic group contains 1-8 carbon atoms. In still other embodiments, the aliphatic group contains 1-6 carbon atoms. In yet other embodiments, the aliphatic group contains 1-4 carbon atoms. In still other embodiments, the aliphatic group contains 1-3 carbon atoms, and in yet other embodiments, the aliphatic group contains 1-2 carbon atoms. Some non-limiting examples of the aliphatic group include linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. For example,  $(C_1-C_6)$ aliphatic groups include unbranched or branched, unsubstituted or suitably substituted  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl or  $(C_2-C_6)$ alkynyl groups. The aliphatic group herein is optionally substituted independently with one or more substituents described herein.

[062] The term "alkoxy" refers to an alkyl group, as previously defined, attached to the principal carbon atom through an oxygen atom. Unless otherwise specified, the alkoxy group contains 1-20 carbon atoms. In some embodiments, the alkoxy group contains 1-10 carbon atoms. In other embodiments, the alkoxy group contains 1-8 carbon atoms. In still other embodiments, the alkoxy group contains 1-6 carbon atoms. In yet other embodiments, the alkoxy group contains 1-4 carbon atoms, and in further embodiments, the alkoxy group contains 1-3 carbon atoms.

[063] Some non-limiting examples of the alkoxy group include methoxy (MeO, -OCH<sub>3</sub>), ethoxy (EtO, -OCH<sub>2</sub>CH<sub>3</sub>), 1-propoxy (*n*-PrO, *n*-propoxy, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-propoxy (*i*-PrO, *i*-propoxy, -OCH(CH<sub>3</sub>)<sub>2</sub>), 1-butoxy (*n*-BuO, *n*-butoxy, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-methyl-1-propoxy (*i*-BuO, *i*-butoxy, -OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2-butoxy (*s*-BuO, *s*-butoxy, -OCH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 2-methyl-2-propoxy (*t*-BuO, *t*-butoxy, -OC(CH<sub>3</sub>)<sub>3</sub>), 1-pentoxy (*n*-pentoxy, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-pentoxy (-OCH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-pentoxy (-OCH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2-methyl-2-butoxy (-OC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-methyl-2-butoxy (-OCH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>), 3-methyl-1-butoxy (-OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2-methyl-1-butoxy (-OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), and the like. The alkoxy group herein is optionally substituted independently with one or more substituents described herein.

[064] The term "haloalkyl", "haloalkenyl" or "haloalkoxy" refers to alkyl, alkenyl, or alkoxy, as the case may be, substituted with one or more halogen atoms.

[065] The term "alkylamino" embraces "*N*-alkylamino" and "*N,N*-dialkylamino" where amino groups are independently substituted with one alkyl radical or with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable alkylamino radicals may be mono or dialkylamino such as *N*-methylamino, *N*-ethylamino, *N,N*-dimethylamino, *N,N*-diethylamino and the like. The alkylamino group herein is optionally substituted independently with one or more substituents described herein.

[066] The term "arylamino" refers to 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.

and 1 to 3 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO<sub>2</sub>, PO or PO<sub>2</sub>) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO<sub>2</sub>, PO or PO<sub>2</sub>).

[071] The heterocyclyl may be a carbon radical or heteroatom radical. Some non-limiting examples of the heterocyclic ring include pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homo-piperazinyl, azetidyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2*H*-pyranyl, 4*H*-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, and 1,2,3,4-tetrahydro iso-quinolinyl. Some non-limiting examples of the heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidindionyl and 1,1-dioxo-thiomorpholinyl.

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

[073] The term "halogen" refers to Fluoro (F), Chloro (Cl), Bromo (Br), or Iodo (I).

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

[075] The term "D" or "<sup>2</sup>H" denotes a single deuterium atom. One of this radical may be attached, for example, to a methyl group to form a mono-deuterated methyl group (CDH<sub>2</sub>), two of deuterium atoms may be attached to a methyl group to form a di-deuterated methyl (CD<sub>2</sub>H), and three of deuterium atoms may be attached to a methyl group to form a tri-deuterated methyl group (CD<sub>3</sub>).

[076] The term "azido" or "N<sub>3</sub>" refers to an azide moiety. This radical may be attached,

for example, to a methyl group to form azidomethane (methyl azide,  $\text{MeN}_3$ ); or attached to a phenyl group to form phenyl azide ( $\text{PhN}_3$ ).

[077] The term "aryl" refers to monocyclic, bicyclic, and tricyclic carbocyclic ring systems having a total of 6 to 14 ring members, preferably, 6 to 12 ring members, and more preferably 6 to 10 ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3 to 7 ring members and that has one or more points of attachment to the rest of the molecule. The term "aryl" may be used interchangeably with the term "aryl ring" or "aromatic ring". Some non-limiting examples of the aryl group include phenyl, naphthyl, and anthracenyl. The aryl radical is optionally substituted independently with one or more substituents described herein.

[078] The term "heteroaryl" 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, and at least one aromatic ring in the system contains one or more heteroatoms, wherein each ring in the system contains 5 to 7 ring members and that has one or more points of attachment to the rest of the molecule. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic ring". In some embodiments, the 5-10 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms independently selected from O, S and N. In other embodiments, the 5-6 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms independently selected from O, S and N. The heteroaryl radical is optionally substituted independently with one or more substituents described herein.

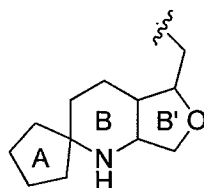
[079] Some non-limiting examples of the heteroaryl group include the following monocycles: 2-furanyl, 3-furanyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 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, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl,

pyrazinyl, 1,3,5-triazinyl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), purinyl, quinoliny (e.g., 2-quinoliny, 3-quinoliny, 4-quinoliny), and isoquinoliny (e.g., 1-isoquinoliny, 3-isoquinoliny or 4-isoquinoliny), imidazo[1,2-*a*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidyl, imidazo[1,2-*b*]pyridaziny, [1,2,4]triazolo[4,3-*b*]pyridaziny, [1,2,4]triazolo[1,5-*a*]pyrimidiny, or [1,2,4]triazolo[1,5-*a*]pyridyl.

[080] The term "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", refers to -CO<sub>2</sub>H. The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-.

[081] The term "fused bicyclic ring", "fused cyclic", "fused bicycyl" or "fused cyclyl" as used interchangeably refers to a monovalent or multivalent saturated or partially unsaturated bridged ring system, which refers to a bicyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon).

[082] The term "spirocyclyl", "spirocyclic", "spiro bicycyl" or "spiro bicyclic" as used interchangeably refers to a monovalent or multivalent, saturated or partially unsaturated ring system wherein a ring originating from a particular annular carbon of another ring. For example, as depicted below in Structure a, a saturated bridged ring system (ring B and B') is termed as "fused bicyclic", whereas ring A and ring B share an atom between the two saturated ring system, which terms as a "spirocyclyl" or "spiro bicycyl". Each ring in the fused bicycyl or the spiro bicycyl can be either a carbocyclyl or a heterocyclyl, and each ring is optionally substituted independently with one or more substituents described herein.



Structure a

[083] The term "heterocycloalkyl" refers to a monovalent or multivalent saturated ring having 3 to 12 ring atoms as a monocyclic, bicyclic, or tricyclic ring system in which at least one ring atom is selected from nitrogen, sulfur and oxygen.

[084] The term "n membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6 membered heterocycloalkyl and 1,2,3,4-tetrahydro-naphthalenyl is an example of a 10 membered cycloalkyl group.

[085] The term "unsaturated" refers to a moiety having one or more units of unsaturation.

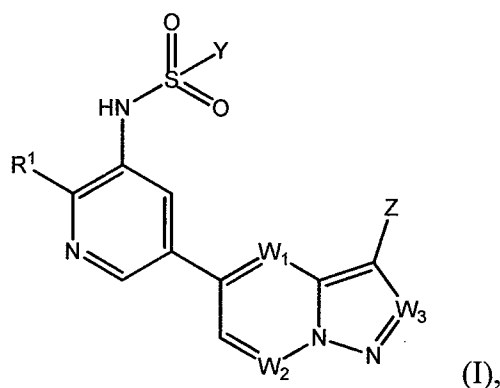
[086] The term "protecting group" or "PG" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxy-carbonyl (BOC, Boc), benzyloxycarbonyl (CBZ, Cbz) and 9-fluorenylmethylenoxy-carbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include -CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub>Ph, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl) ethoxy-methyl, 2-(*p*-toluenesulfonyl) ethyl, 2-(*p*-nitrophenylsulfonyl)-ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see Greene et al., "Protective Groups in Organic Synthesis," John Wiley & Sons, New York, **1991** and Kocienski et al., "Protecting Groups," Thieme, Stuttgart, **2005**.

[087] The term "prodrug" refers to a compound that is transformed in vivo into a compound of formula (I). Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C<sub>1</sub>-C<sub>24</sub>) 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

colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

## DESCRIPTION OF COMPOUNDS OF THE INVENTION

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



or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a solvate, a metabolite, a pharmaceutically salt or a prodrug thereof, wherein each of Y, R<sup>1</sup>, Z, W<sub>1</sub>, W<sub>2</sub> and W<sub>3</sub> is as defined herein.

[098] In certain embodiments, each of W<sub>1</sub>, W<sub>2</sub> and W<sub>3</sub> is independently N or CR<sup>c</sup>;

Z is D, CN, N<sub>3</sub>, or  $\text{---}\text{X}$ ;

X is H, D, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, (C<sub>6</sub>-C<sub>10</sub>)aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N<sub>3</sub>, OR<sup>a</sup>, SR<sup>a</sup>, NR<sup>a</sup>R<sup>b</sup>, -C(=O)NR<sup>a</sup>R<sup>b</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)haloalkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-CN, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-OR<sup>a</sup>, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-NR<sup>a</sup>R<sup>b</sup>, (C<sub>6</sub>-C<sub>10</sub>)aryl, and 5-10 membered heteroaryl;

<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.

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

[151] 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, aminogluthethimide, 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.

[152] 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. Oncol.*, **2003**, 21(4), 646-651), tositumomab (BEXXAR<sup>®</sup>), 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).

[175] 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.

[176] Column chromatography was conducted using a silica gel column. Silica gel (300-400 mesh) was purchased from Qingdao Ocean Chemical Factory.  $^1\text{H}$  NMR spectra were recorded with a Bruker 400 MHz spectrometer or a Bruker 600 MHz spectrometer at ambient temperature.  $^1\text{H}$  NMR spectra were obtained as  $\text{CDCl}_3$ ,  $\text{DMSO}-d_6$ ,  $\text{CD}_3\text{OD}$  or acetone- $d_6$  solutions (reported in ppm), using TMS (0 ppm) or chloroform (7.26 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[177] Low-resolution mass spectral (MS) data were generally determined on an Agilent 6120 Quadrupole HPLC-MS (Zorbax SB-C18, 2.1 x 30 mm, 3.5 micron, 6 minutes run, 0.6 mL/min flow rate, 5% to 95% (0.1% formic acid in  $\text{CH}_3\text{CN}$ ) in (0.1% formic acid in  $\text{H}_2\text{O}$ )) with UV detection at 210 nm/254 nm and electrospray ionization mode (ESI).

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

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

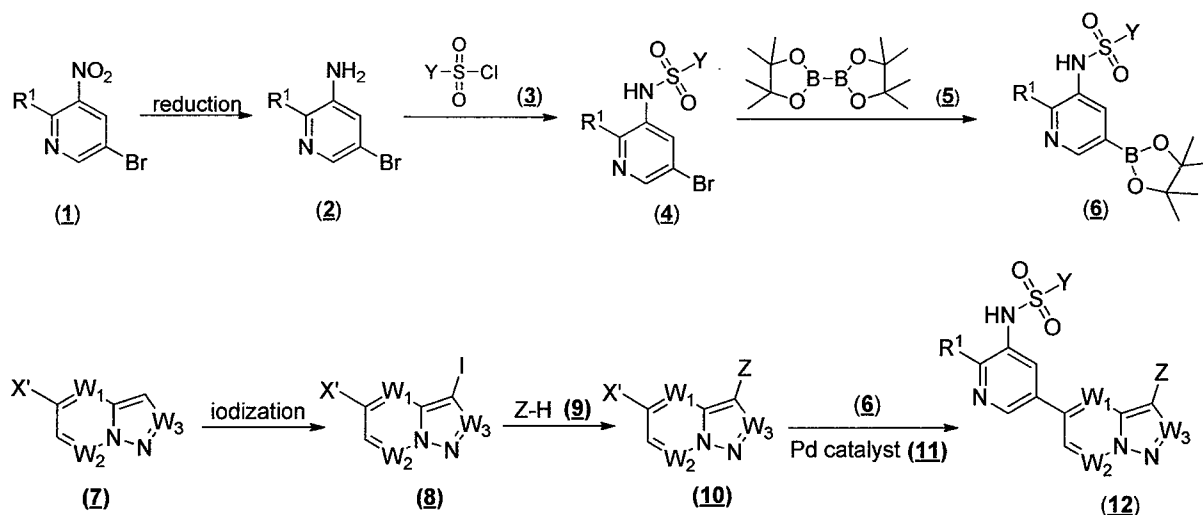
$\text{Ac}_2\text{O}$  acetic anhydride  
 $\text{BBr}_3$  boron tribromide  
BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl  
BOC, Boc butyloxycarbonyl  
BSA bovine serum albumin  
 $\text{CDCl}_3$  chloroform deuterated  
 $\text{CHCl}_3$  chloroform  
 $\text{CH}_2\text{Cl}_2$ , DCM methylene chloride  
 $\text{CH}_3\text{SO}_2\text{Cl}$ , MsCl methanesulfonyl chloride

$\text{H}_2\text{O}_2$  hydrogen peroxide  
 $\text{HOAc}$ ,  $\text{AcOH}$  acetic acid  
 $\text{HOBt}$  1-hydroxybenzotriazole hydrate  
*i*- $\text{Pr}_2\text{NH}$  diisopropylamine  
 $\text{K}_2\text{CO}_3$  potassium carbonate  
 $\text{KOH}$  potassium hydroxide  
 $\text{LiHMDS}$  lithium bis(trimethylsilyl)amide  
 $\text{LDA}$  Lithium diisopropylamide  
 $\text{MCPBA}$  *meta*-chloroperbenzoic acid  
 $\text{MeCN}$ ,  $\text{CH}_3\text{CN}$  acetonitrile  
 $\text{MeI}$  methyl iodide  
 $\text{MeOH}$ ,  $\text{CH}_3\text{OH}$  methanol  
 $2\text{-MeTHF}$  2-methyl tetrahydrofuran  
 $\text{MgSO}_4$  magnesium sulfate  
 $\text{mL}$ ,  $\text{ml}$  milliliter  
 $\text{min}$  minute  
 $\text{N}_2$  nitrogen  
 $\text{NaBH}_4$  sodium borohydride  
 $\text{NaBH}_3\text{CN}$  sodium cyanoborohydride  
 $\text{NaCl}$  sodium chloride  
 $\text{NaClO}_2$  sodium chlorite  
 $\text{NaH}$  sodium hydride  
 $\text{Na}_2\text{CO}_3$  sodium carbonate  
 $\text{NaHCO}_3$  sodium bicarbonate  
 $\text{NaH}_2\text{PO}_4$  sodium biphosphate  
 $\text{NaI}$  sodium iodide  
 $\text{NaO}(t\text{-Bu})$  sodium *tert*-butoxide  
 $\text{NaOH}$  sodium hydroxide  
 $\text{Na}_2\text{SO}_4$  sodium sulfate



[180] Representative synthetic procedures for the preparation of compounds disclosed herein are outlined below in following schemes. Unless otherwise indicated,  $R^1$ ,  $W_1$ ,  $W_2$ ,  $W_3$ ,  $Y$  and  $Z$  carry the definitions set forth above in connection with formula (I).  $X'$  is Cl, Br, or I.

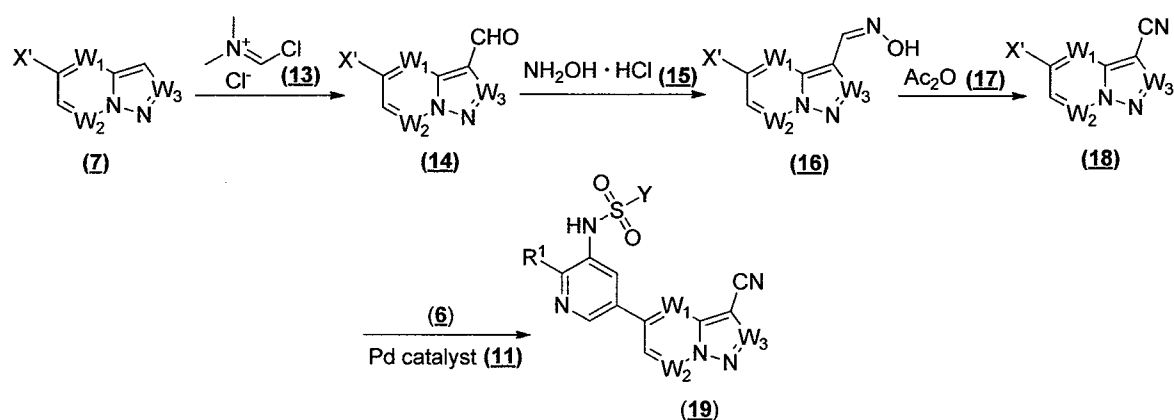
Scheme 1



[181] Some compounds with structures as defined in Formula (I) can be prepared in a general method illustrated in Scheme 1. The nitro-pyridine derivative (**1**) is converted to an amino-pyridine (**2**) under a reducing condition such as hydrogenation in the presence of a catalyst Pd/C or Fe powder in aqueous acidic conditions. Compound (**2**) can then be coupled with sulfonyl chloride (**3**) to give sulfonamide (**4**) in the presence of a base such as  $\text{Na}_2\text{CO}_3$ ,  $\text{Et}_3\text{N}$ , or pyridine in an aprotic solvent (for example,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , etc.), or in pyridine with catalytic amount of DMAP, or under the **Schotten–Baumann condition**. The subsequent coupling of (**4**) with bis(pinacolato)diboron (**5**) in the presence of an appropriate Pd catalyst leads to boronic ester (**6**).

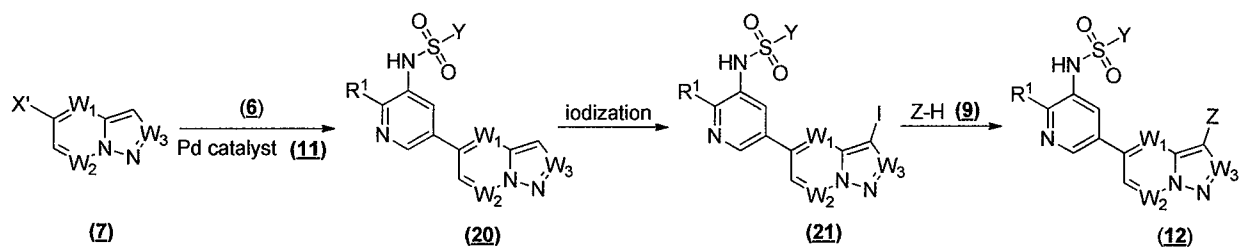
[182] The synthesis of compound (**12**) is also demonstrated in Scheme 1. The iodination of halogenated compound (**7**) with *N*-iodosuccinimide at room temperature affords iodo compound (**8**). Iodo compound (**8**) is then coupled with compound (**9**) (i.e., acetylene derivatives, cyanide or azide) to give the intermediate (**10**) under either basic conditions or in the presence of a Pd catalyst. The desired kinase inhibitors (**12**) are obtained by the coupling of compound (**10**) with the boronic ester (**6**) in the presence of an appropriate Pd catalyst (**11**).

## Scheme 2



[183] Alternatively, the compounds disclosed herein can be prepared by the method as described in Scheme 2. Compound (7) is first treated with (chloromethylene)dimethyliminium chloride (13) to afford aldehyde (14). Compound (14) is condensed with hydroxylamine hydrochloride (15) to give oxime (16), which is further reacted with acetic anhydride (17) leading to nitrile (18). Coupling of nitrile (18) with boronic ester (6) in the presence of an appropriate Pd catalyst (11) furnishes the desired kinase inhibitors (19).

## Scheme 3



[184] Scheme 3 shows another method of preparing the kinase inhibitors disclosed herein. The coupling of halogenated compound (7) with the boronic ester (6) in the presence of an appropriate Pd catalyst can give compound (20). The subsequent iodination of compound (20) with *N*-iodosuccinimide can afford compound (21). Coupling of compound (21) with compound (9) (i.e., acetylene derivatives, cyanide or azide) under either basic conditions or in the presence of a Pd catalyst affords the desired kinase inhibitors (12).

## EXAMPLES

Example 1 2,4-difluoro-*N*-(5-(3-(3-hydroxyprop-1-yn-1-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

dissolved in MeOH (100 mL) and NaOH (2.50 g, 60 mmol). The resulted mixture was stirred at rt for 12 hours and concentrated *in vacuo*. The residue was dissolved in H<sub>2</sub>O (50 mL) and the resulted mixture was extracted with DCM (100 mL x 3). The combined organic phases were washed with brine (100 mL x 3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give the title compound as a brown solid (16.90 g, 89.1%).

MS (ESI, pos. ion) m/z: 379.0 [M-+-H]<sup>+</sup>.

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

[188] To a suspension of N-(5-bromo-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (16.90 g, 44.6 mmol) in 1,4-dioxane (300 mL) was added bis(pinacolato)diboron (13.59 g, 53.5 mmol), followed by the addition of Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (3.67 g, 4.5 mmol) and potassium acetate (13.12 g, 133.8 mmol). The reaction mixture was degassed with N<sub>2</sub> for 3 times, then heated to 90 °C and stirred further for 7 hours. The mixture was then cooled to rt, quenched with H<sub>2</sub>O (100 mL) and extracted with EtOAc (500 mL x 3). The combined organic phases were washed with brine (500 mL x 3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give the title compound as a pale yellow solid (24.00 g, 100%).

MS (ESI, pos. ion) m/z: 427.0 [M-+-H]<sup>+</sup>;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 8.25 (d, *J* = 1.0 Hz, 1H), 8.04 (s, 1H), 7.85 (m, 1H), 7.14 (s, 1H), 6.93 (m, 2H), 3.91 (s, 3H), 1.33 (s, 12H).

Step 5) 5-chloro-3-iodopyrazolo[1,5-*a*]pyrimidine

[189] To a solution of 5-chloropyrazolo[1,5-*a*]pyrimidine (200 mg, 1.30 mmol) in DMF (2 mL) was added N-iodosuccinimide (322 mg, 1.86 mmol). The reaction was stirred at rt overnight, then diluted with EtOAc (100 mL), and washed with H<sub>2</sub>O (50 mL), saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution (50 mL) and brine (50 mL). The separated organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (EtOAc/PE (v/v) = 1/4) to give the title compound as a pale yellow solid (390 mg, 100%).

MS (ESI, pos. ion)  $m/z$ : 279.9  $[M+H]^+$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.57 (d,  $J = 7.2$  Hz, 1H), 8.16 (s, 1H), 6.86 (d,  $J = 7.2$  Hz, 1H).

Step 6) 3-(5-chloropyrazolo[1,5-*a*]pyrimidin-3-yl)prop-2-yn-1-ol

[190] To a suspension of 5-chloro-3-iodopyrazolo[1,5-*a*]pyrimidine (363 mg, 1.30 mmol),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (91 mg, 0.13 mmol),  $\text{CuI}$  (25 mg, 0.13 mmol) and triethylamine (658 mg, 6.50 mmol) in DMF (15 mL) was added prop-2-yn-1-ol (73 mg, 1.30 mmol). The reaction mixture was degassed with  $\text{N}_2$  for 3 times and stirred at rt for 20 hours, then quenched with  $\text{H}_2\text{O}$  (15 mL) and extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (50 mL x 3), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (EtOAc/PE (v/v) = 1/2) to give the title compound as a yellow solid (220 mg, 81.5%).

MS (ESI, pos. ion)  $m/z$ : 208.0  $[M+H]^+$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.58 (d,  $J = 7.4$  Hz, 1H), 8.23 (s, 1H), 6.90 (d,  $J = 7.2$  Hz, 1H), 4.58 (s, 2H).

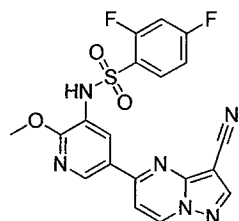
Step 7) 2,4-difluoro-*N*-(5-(3-(3-hydroxyprop-1-yn-1-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide

[191] To a suspension of 3-(5-chloropyrazolo[1,5-*a*]pyrimidin-3-yl)prop-2-yn-1-ol (208 mg, 1 mmol), 2,4-difluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (618 mg, 1.5 mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$  (82 mg, 0.1 mmol) in DME (20 mL) was added a solution of  $\text{Na}_2\text{CO}_3$  (318 mg, 3 mmol) in  $\text{H}_2\text{O}$  (2.5 mL). The reaction mixture was degassed with  $\text{N}_2$  for 3 times, then heated to 100 °C and stirred further for 5 hours. The mixture was cooled to rt, quenched with  $\text{H}_2\text{O}$  (20 mL), and extracted with EtOAc (500 mL x 3). The combined organic phases were washed with brine (50 mL x 3), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (EtOAc/PE (v/v) = 1/2) to give the title compound as a yellow solid (80 mg, 17%).

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

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 10.46 (s, 1H), 9.23 (d, *J* = 7.4 Hz, 1H), 8.88 (d, *J* = 1.7 Hz, 1H), 8.42 (d, *J* = 2.1 Hz, 1H), 8.41 (s, 1H), 7.82 (dd, *J* = 8.4, 6.2 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.59 (td, *J* = 10.0, 2.2 Hz, 1H), 7.24 (td, *J* = 8.6, 2.0 Hz, 1H), 5.38 (t, *J* = 5.9 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 2H), 3.72 (s, 3H).

Example 2      *N*-(5-(3-cyanopyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide



Step 1) 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde

[192]      To a solution of 5-chloropyrazolo[1,5-*a*]pyrimidine (295 mg, 1.92 mmol) in DCM (10 mL) was added (chloromethylene)dimethyliminium chloride (1.06 g, 6 mmol). The reaction was stirred at 45 °C overnight, and concentrated *in vacuo*. The residue was dissolved in saturated NaHCO<sub>3</sub> aqueous solution (50 mL) and the resulted mixture was then extracted with EtOAc (50 mL x 3). The combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give the title compound as a light yellow solid (380 mg, 100%).

MS (ESI, pos. ion) *m/z*: 182.2 [M+H]<sup>+</sup>.

Step 2) (*E*)-5-chloropyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde oxime

[193]      To a suspension of 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde (380 mg, 2.1 mmol) in EtOH (20 mL) and H<sub>2</sub>O (10 mL) was added hydroxylamine hydrochloride (220 mg, 3.15 mmol). The reaction was stirred at 85 °C for 2 hours, and then concentrated *in vacuo*. The residue was adjusted to pH=7 with saturated NaHCO<sub>3</sub> aqueous solution. The resulted mixture was filtered and the filter cake was dried *in vacuo* to give the title compound as a yellow solid (280 mg, 74.4%).

MS (ESI, pos. ion) *m/z*: 197.1 [M+H]<sup>+</sup>.

Step 3) 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile

[194]      A solution of (*E*)-5-chloropyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde oxime (280

mg, 1.42 mmol) in Ac<sub>2</sub>O (20 mL) was stirred at 140 °C for 18 hours, then cooled to rt and concentrated *in vacuo*. The residue was washed with Et<sub>2</sub>O (20 mL) to give the title compound as a yellow solid (106 mg, 42%).

MS (ESI, pos. ion) *m/z*: 179.1 [M+H]<sup>+</sup>.

Step 4) N-(5-(3-cyanopyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

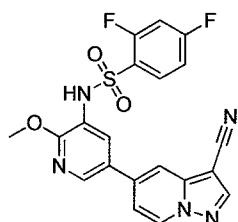
[195] 2,4-difluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (383 mg, 0.9 mmol), 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (106 mg, 0.6 mmol), Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (49 mg, 0.06 mmol) and Na<sub>2</sub>CO<sub>3</sub> (254 mg, 2.5 mmol) were placed into a two-neck flask, then degassed with N<sub>2</sub> for 3 times, and followed by adding 1,4-dioxane (12 mL) and water (2 mL). The mixture was degassed with N<sub>2</sub> for 3 times again, then heated to 90 °C and stirred further for 5 hours. The mixture was cooled to rt, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/3) to give the title compound as a light yellow solid (200 mg, 75.3%).

HPLC: 97%;

MS (ESI, pos. ion) *m/z*: 443.2 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 10.51 (s, 1H), 9.41 (d, *J* = 7.4 Hz, 1H), 8.93 (d, *J* = 2.1 Hz, 1H), 8.81 (s, 1H), 8.45 (d, *J* = 2.2 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.85-7.78 (m, 1H), 7.61-7.52 (m, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 3.77 (s, 3H).

Example 3 N-(5-(3-cyanopyrazolo[1,5-*a*]pyridin-5-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide



Step 1) 5-bromopyrazolo[1,5-*a*]pyridine

[196] A solution of ethyl 5-bromopyrazolo[1,5-*a*]pyridine-3-carboxylate (240 mg, 0.89

mmol) in 40% H<sub>2</sub>SO<sub>4</sub> (12 mL) was stirred at 100 °C for 4 hours, then cooled to rt, and neutralized to pH=7 with aq. NaOH (6 M) in ice bath. The resulted mixture was extracted with DCM (25 mL x 2). The combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give the title compound as a light yellow solid (175 mg, 99.5%).

MS (ESI, pos. ion) m/z: 196.9 [M+H]<sup>+</sup>.

#### Step 2) 5-bromopyrazolo[1,5-*a*]pyridine-3-carbaldehyde

[197] To a solution of 5-bromopyrazolo[1,5-*a*]pyridine (175 mg, 0.89 mmol) in DCM (6 mL) was added (chloromethylene)dimethyliminium chloride (632 mg, 3.56 mmol). The reaction was stirred at 44 °C overnight, and concentrated *in vacuo*. The residue was dissolved in saturated NaHCO<sub>3</sub> aqueous solution (25 mL) and the resulted mixture was then extracted with EtOAc (25 mL x 3). The combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give the title compound as a light yellow solid (225 mg, 100%).

MS (ESI, pos. ion) m/z: 225.0 [M+H]<sup>+</sup>.

#### Step 3) (*E*)-5-bromopyrazolo[1,5-*a*]pyridine-3-carbaldehyde oxime

[198] To a suspension of 5-bromopyrazolo[1,5-*a*]pyridine-3-carbaldehyde (225 mg, 1 mmol) in EtOH (10 mL) and H<sub>2</sub>O (5 mL) was added hydroxylamine hydrochloride (104 mg, 1.5 mmol). The reaction was stirred at 85 °C for 2 hours, then cooled to rt, and concentrated *in vacuo*. The residue was adjusted to pH=7 with saturated NaHCO<sub>3</sub> aqueous solution. The resulted mixture was then filtered and the filter cake was dried *in vacuo* to give title compound as a yellow solid (240 mg, 99%).

MS (ESI, pos. ion) m/z: 240.0 [M+H]<sup>+</sup>.

#### Step 4) 5-bromopyrazolo[1,5-*a*]pyridine-3-carbonitrile

[199] A solution of (*E*)-5-bromopyrazolo[1,5-*a*]pyridine-3-carbaldehyde oxime (240 mg, 1 mmol) in Ac<sub>2</sub>O (6 mL) was stirred at 140 °C for 18 hours, then cooled to rt, and concentrated *in vacuo*. The residue was washed with Et<sub>2</sub>O (1 mL) to give the title compound as a yellow solid (44 mg, 22.5%).

MS (ESI, pos. ion) m/z: 222.0 [M+H]<sup>+</sup>.

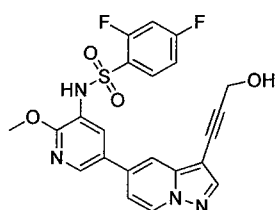
Step 5) N-(5-(3-cyanopyrazolo[1,5-a]pyridin-5-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[200] 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (612 mg, 1.5 mmol), 5-bromopyrazolo[1,5-a]pyridine-3-carbonitrile (222 mg, 1 mmol), Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (16 mg, 0.02 mmol) and Na<sub>2</sub>CO<sub>3</sub> (85 mg, 0.8 mmol) were placed into a two-neck flask, then degassed with N<sub>2</sub> for 3 times, and followed by adding 1,4-dioxane (5 mL) and water (1 mL). The resulted mixture was degassed with N<sub>2</sub> for 3 times, then heated to 90 °C and stirred further for 5 hours. The mixture was cooled to rt and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a light yellow solid (400 mg, 81.6%).

MS (ESI, pos. ion) m/z: 442.0 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 10.37 (s, 1H), 9.02 (d, *J* = 7.2 Hz, 1H), 8.67 (s, 1H), 8.60 (d, *J* = 2.2 Hz, 1H), 8.26-8.16 (m, 2H), 7.82-7.72 (m, 1H), 7.57 (dd, *J* = 13.2, 5.8 Hz, 2H), 7.21 (t, *J* = 8.5 Hz, 1H), 3.67 (s, 3H).

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



Step 1) 5-bromopyrazolo[1,5-a]pyridine

[201] A solution of ethyl 5-bromopyrazolo[1,5-a]pyridine-3-carboxylate (1.2 g, 4.46 mmol) in 40% H<sub>2</sub>SO<sub>4</sub> (60 mL) was stirred at 100 °C for 4 hours, then cooled to rt, and neutralized to pH=7 with aq. NaOH (6 M) in ice bath. The resulted mixture was extracted with DCM (120 mL x 2). The combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give the title compound as a light yellow solid (900 mg, 100%).

MS (ESI, pos. ion) m/z: 196.9 [M+H]<sup>+</sup>.

Step 2) 5-bromo-3-iodopyrazolo[1,5-a]pyridine

[202] To a solution of 5-bromopyrazolo[1,5-*a*]pyridine (900 mg, 4.46 mmol) in methanol (100 mL) was added N-iodosuccinimide (1 g, 4.46 mmol) slowly at -10 °C. The mixture was stirred at -10 °C for 0.5 hour, then warmed to rt and stirred further for 18 hours. The mixture was concentrated *in vacuo*, and the residue was dissolved in DCM (200 mL). The resulted mixture was washed with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution (200 mL). The separated organic phase was concentrated *in vacuo* to give the title compound as a light pink solid (1.4 g, 97.5%).

MS (ESI, pos. ion) *m/z*: 322.8 [M+H]<sup>+</sup>.

Step 3) 3-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)prop-2-yn-1-ol

[203] A mixture of 5-bromo-3-iodopyrazolo[1,5-*a*]pyridine (644 mg, 2 mmol), prop-2-yn-1-ol (112 mg, 2 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (140 mg, 0.2 mmol), CuI (38 mg, 0.2 mmol), and diisopropylethylamine (645 mg, 5 mmol) in DMF (32 mL) was stirred at rt under N<sub>2</sub> atmosphere for 3 hours, then diluted with H<sub>2</sub>O (200 mL), and extracted with EtOAc (200 mL x 3). The combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (pure DCM) to give the title compound as a yellow solid (200 mg, 4%).

MS (ESI, pos. ion) *m/z*: 251.0 [M+H]<sup>+</sup>.

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

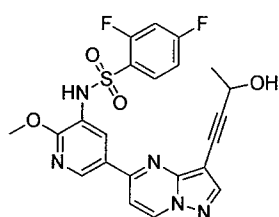
[204] 2,4-difluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (509 mg, 1.2 mmol), 3-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)prop-2-yn-1-ol (200 mg, 0.8 mmol), Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (65 mg, 0.08 mmol) and Na<sub>2</sub>CO<sub>3</sub> (339 mg, 3.2 mmol) were placed into a two-neck flask, and the mixture was degassed with N<sub>2</sub> for 3 times, followed by adding 1,4-dioxane (15 mL) and water (2.5 mL). The resulted mixture was degassed with N<sub>2</sub> for 3 times again. The mixture was heated to 90 °C and stirred further for 5 hours, then cooled to rt, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a white solid (122 mg, 32.5%).

HPLC: 91%;

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

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm): 10.37 (s, 1H), 8.83 (d,  $J = 7.2$  Hz, 1H), 8.53 (d,  $J = 2.3$  Hz, 1H), 8.23 (s, 1H), 8.05 (d,  $J = 2.3$  Hz, 1H), 7.87 (s, 1H), 7.77 (dd,  $J = 14.8, 8.5$  Hz, 1H), 7.59 (dd,  $J = 13.9, 5.9$  Hz, 1H), 7.33 (dd,  $J = 7.3, 1.9$  Hz, 1H), 7.22 (t,  $J = 8.4$  Hz, 1H), 5.33 (t,  $J = 5.9$  Hz, 1H), 4.39 (d,  $J = 5.8$  Hz, 2H), 3.67 (s, 3H).

Example 5 2,4-difluoro-*N*-(5-(3-(3-hydroxybut-1-yn-1-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 2,4-difluoro-*N*-(2-methoxy-5-(pyrazolo[1,5-*a*]pyrimidin-5-yl)pyridin-3-yl)benzenesulfonamide

[205] To a mixture of 5-chloropyrazolo[1,5-*a*]pyrimidine (0.46 g, 3.0 mmol) in 60 mL DME were added  $\text{Pd}(\text{dppf})_2\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$  (0.25 g, 0.3 mmol) and a solution of sodium carbonate (0.95 g, 9.0 mmol) in water (8 mL). The mixture was purged with nitrogen several times and then stirred at room temperature for a while. To the resulted solution was added 2,4-difluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzene sulfonamide (1.53 g, 3.6 mmol). The mixture was purged with nitrogen again and stirred at 100 °C for 6 hours, then cooled to rt, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a yellow solid (1.24 g, 100%).

MS (ESI, pos. ion)  $m/z$ : 418.2  $[M+H]^+$ .

Step 2) 2,4-difluoro-*N*-(5-(3-iodopyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[206] To a solution of 2,4-difluoro-*N*-(2-methoxy-5-(pyrazolo[1,5-*a*]pyrimidin-5-yl)pyridin-3-yl)benzenesulfonamide (1.98 g, 10.0 mmol) in methanol (50 mL) was added *N*-iodosuccinimide (2.47 g, 11.0 mmol) portionwise at rt. The mixture was stirred at 45 °C for 10

hours, then concentrated *in vacuo*, and the residue was diluted with H<sub>2</sub>O (40 mL). The resulted mixture was stirred at rt over 2 hours, then filtered, and the collected solid was diluted with PE/EtOAc (40 mL/4 mL). The resulted suspension was stirred at rt for 1 hour, and then filtered to give the title compound as a pale yellow solid (1.05 g, 80.57%).

MS (ESI, pos. ion) *m/z*: 544.0 [M+H]<sup>+</sup>.

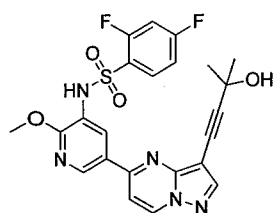
Step 3) 2,4-difluoro-*N*-(5-(3-(3-hydroxybut-1-yn-1-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[207] To a suspension of 2,4-difluoro-*N*-(5-(3-iodopyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (2.32 g, 4.27 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.31 g, 0.43 mmol) and CuI (82 mg, 0.43 mmol) in 15 mL DMF was added triethylamine (2.15 g, 21.3 mmol). After the mixture was purged with nitrogen several times, but-3-yn-2-ol (1.08 g, 15.4 mmol) was added via a syringe. The mixture was stirred at 50 °C under N<sub>2</sub> atmosphere for 6 hours, then quenched with water (40 mL), and the resulted mixture was stirred over 1 hour. Filtered and the filter cake was purified by a silica gel column chromatography (EtOAc/PE (v/v) = 1/2) to provide the crude product, which was diluted with a mixture of DCM/MeOH/PE (15 mL/3 mL/65 mL). The resulted mixture was stirred at rt over 2 hours, and then filtered to give the title compound as a pale yellow solid (1.01 g, 48.77%).

MS (ESI, neg. ion) *m/z*: 484.1 [M-H]<sup>-</sup>;

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 10.45 (s, 1H), 9.21 (d, *J* = 7.4 Hz, 1H), 8.88 (d, *J* = 2.0 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.38 (s, 1H), 7.80 (dd, *J* = 14.8, 8.4 Hz, 1H), 7.75 (d, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 8.8 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 4.69 (dd, *J* = 13.1, 6.5 Hz, 1H), 3.72 (s, 3H), 1.45 (d, *J* = 6.6 Hz, 3H).

Example 6 2,4-difluoro-*N*-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



[208] To a mixture of 2,4-difluoro-*N*-(5-(3-iodopyrazolo[1,5-*a*]pyrimidin-5-yl)-

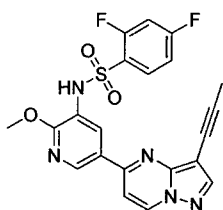
2-methoxypyridin-3-yl)benzenesulfonamide (1.05 g, 1.93 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.136 g, 0.19 mmol) and CuI (37 mg, 0.19 mmol) in 5 mL DMF was added diisopropylethylamine (0.98 g, 7.60 mmol). After the mixture was purged with nitrogen several times, 2-methylbut-3-yn-2-ol (0.49 g, 5.79 mmol) was added via a syringe. The mixture was stirred at 50 °C for 4 hours under N<sub>2</sub> atmosphere. The reaction mixture was concentrated *in vacuo* and quenched with water (25 mL). The resulted mixture was stirred over 1 hour and filtered. The collected solid was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (520 mg, 53.99%).

MS (ESI, neg. ion) m/z: 498.0 [M-H]<sup>-</sup>;

HPLC: 96.74%;

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 10.45 (s, 1H), 9.22 (d, *J* = 7.4 Hz, 1H), 8.89 (d, *J* = 1.8 Hz, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.36 (s, 1H), 7.80 (dd, *J* = 14.8, 8.5 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.65–7.53 (m, 1H), 7.24 (td, *J* = 8.5, 2.3 Hz, 1H), 5.52 (s, 1H), 3.74 (s, 3H), 1.54 (s, 6H).

Example 7 2,4-difluoro-*N*-(2-methoxy-5-(3-(prop-1-yn-1-yl)pyrazolo[1,5-*a*]pyrimidin-5-yl)pyridin-3-yl)benzenesulfonamide

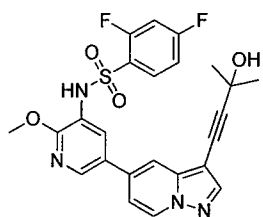


[209] To a mixture of 2,4-difluoro-*N*-(5-(3-iodopyrazolo[1,5-*a*]pyrimidin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (1.50 g, 2.76 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.189 g, 0.27 mmol) and CuI (52 mg, 0.27 mmol) in DMF (20 mL) was added diisopropylethylamine (1.78 g, 13.8 mmol). After the mixture was purged with nitrogen several times, propyne (0.44 g, 11.04 mmol) was added via a syringe. The mixture was stirred at 45 °C for 10 hours under N<sub>2</sub> atmosphere, then concentrated *in vacuo*, and quenched with water (40 mL). The resulted mixture was stirred over 1 hour, then filtered, and the collected solid was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 300/1) to give the title compound as a yellow solid (220 mg, 17.52%).

MS (ESI, pos. ion)  $m/z$ : 456.1  $[M+H]^+$ ;

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

Example 8 2,4-difluoro-*N*-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrazolo[1,5-*a*]pyridin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step 1) 2,4-difluoro-*N*-(2-methoxy-5-(pyrazolo[1,5-*a*]pyridin-5-yl)pyridin-3-yl)benzenesulfonamide

[210] A mixture of 5-bromopyrazolo[1,5-*a*]pyridine (197 mg, 1 mmol), 2,4-difluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzene sulfonamide (639 mg, 1.5 mmol),  $\text{Na}_2\text{CO}_3$  (318 mg, 3.0 mmol) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (35 mg, 0.05 mmol) in 1,4-dioxane/ $\text{H}_2\text{O}$  (5 mL/1 mL) was stirred at 90 °C under nitrogen atmosphere, and the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and extracted with diethyl ether (10 mL). The organic phase was washed with brine (10 mL x 2), dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 30/1) to give the title compound as a white solid (303 mg, 73%).

MS (ESI, pos. ion)  $m/z$ : 416.9  $[M+H]^+$ .

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

[211] To a solution of 2,4-difluoro-*N*-(2-methoxy-5-(pyrazolo[1,5-*a*]pyridin-5-yl)pyridin-3-yl)benzenesulfonamide (2.3 g, 5.52 mmol) in DMF (10 mL) was added *N*-iodosuccinimide (1.3 g, 5.8 mmol) portionwise at rt. The reaction mixture was stirred at rt for 1.0 hour, then quenched with saturated  $\text{Na}_2\text{S}_2\text{O}_3$  aqueous solution (10 mL), and the resulted mixture was

filtered to give the title compound as a white solid (2.87 g, 96%).

MS (ESI, pos. ion)  $m/z$ : 542.9  $[M+H]^+$ ;

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.52 (d,  $J = 7.2$  Hz, 1H), 8.19 (d,  $J = 2.2$ , 1H), 8.03–7.98 (m, 2H), 7.97–7.91 (m, 1H), 7.49 (d,  $J = 1.0$  Hz, 1H), 7.32 (s, 1H), 7.05–6.91 (m, 2H), 4.00 (s, 3H), 2.80 (s, 1H).

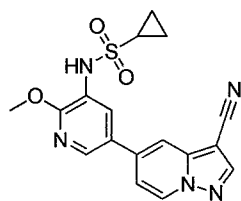
Step 3) 2,4-difluoro-*N*-(5-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrazolo[1,5-*a*]pyridin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[212] A mixture of 2,4-difluoro-*N*-(5-(3-iodopyrazolo[1,5-*a*]pyridin-5-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (1.0 g, 1.85 mmol), 2-methylbut-3-yn-2-ol (0.23 g, 2.76 mmol),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (0.13 g, 0.19 mmol),  $\text{CuI}$  (36 mg, 0.19 mmol), and diisopropylethylamine (0.74g, 0.57 mmol) in DMF (20 mL) was stirred at rt for 3 hours under  $\text{N}_2$  atmosphere. Then the mixture was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 10/1) to give the title compound as a pale yellow solid (0.42 g, 46%).

MS (ESI, pos. ion)  $m/z$ : 499.0  $[M+H]^+$ ;

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.52 (d,  $J = 6.1$  Hz, 1H), 8.20 (d,  $J = 2.1$  Hz, 1H), 8.08 (s, 1H), 8.03 (d,  $J = 2.1$  Hz, 1H), 7.92 (dd,  $J = 14.5, 8.3$  Hz, 1H), 7.68 (s, 1H), 7.59–7.52 (m, 1H), 7.51–7.42 (m, 1H), 7.05–6.94 (m, 2H), 4.00 (s, 3H), 1.60 (s, 6H).

Example 9 *N*-(5-(3-cyanopyrazolo[1,5-*a*]pyridin-5-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide



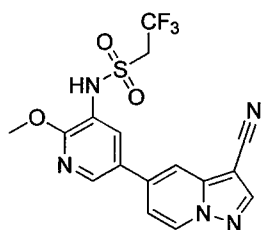
[213] To a solution of 5-bromopyrazolo[1,5-*a*]pyridine-3-carbonitrile (50 mg, 0.225 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) were added *N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)cyclopropanesulfonamide (96 mg, 0.270 mmol),  $\text{Na}_2\text{CO}_3$  (48 mg, 0.45 mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$  (37 mg, 0.045 mmol) under  $\text{N}_2$  atmosphere. The reaction was stirred at 90 °C for 3.5 hours under  $\text{N}_2$  atmosphere, then cooled

to rt and stirred overnight. The mixture was diluted with EtOAc (30 mL), filtered through a pad of CELITE<sup>®</sup>, and the filter cake was washed with EtOAc (20 mL). The filtrate was washed with H<sub>2</sub>O (30 mL) and brine (30 mL). Then the separated organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/EtOAc (v/v) = 10/1) to give the title compound as a white solid (55 mg, 66%).

MS (ESI, pos. ion) *m/z*: 370.0 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.61 (d, *J* = 7.26 Hz, 1H), 8.27-8.25 (m, 2H), 8.09 (d, *J* = 2.07 Hz, 1H), 7.87 (s, 1H), 7.21 (dd, *J* = 1.77, 7.35 Hz, 1H), 6.80 (br s, 1H), 4.11 (s, 3H), 2.60-2.51 (m, 1H), 1.33-1.22 (m, 2H), 1.07-0.99 (m, 2H).

Example 10 *N*-(5-(3-cyanopyrazolo[1,5-*a*]pyridin-5-yl)-2-methoxypyridin-3-yl)-2,2,2-trifluoroethanesulfonamide



Step 1) *N*-(5-bromo-2-methoxypyridin-3-yl)-2,2,2-trifluoroethanesulfonamide

[214] To a solution of 5-bromo-2-methoxypyridin-3-amine (500 mg, 2.46 mmol) in pyridine (10 mL) was added 2,2,2-trifluoroethanesulfonyl chloride (898 mg, 4.92 mmol) dropwise. The reaction was stirred at rt for 18 hours, then concentrated *in vacuo*, and the residue was diluted with water (30 mL). The resulted mixture was extracted with DCM (20 mL x 3). The combined organic phases were washed with water (25 mL x 2) and brine (25 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give the title compound as a yellow solid (859 mg, 100%) which was directly used in the next step reaction without further purification.

MS (ESI, pos. ion) *m/z*: 348.9 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.03 (d, *J* = 2.19 Hz, 1H), 7.91 (d, *J* = 2.22 Hz, 1H), 7.00 (br s, 1H), 4.00 (s, 3H), 3.87 (q, *J* = 8.73 Hz, 2H).

Step 2) 2,2,2-trifluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl))

pyridin-3-yl)ethanesulfonamide

[215] A mixture of *N*-(5-bromo-2-methoxypyridin-3-yl)-2,2,2-trifluoroethanesulfonamide (500 mg, 1.43 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.45 g, 5.729 mmol) and KOAc (562 mg, 5.729 mmol) in 1,4-dioxane (10 mL) was purged with nitrogen several times, and then Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (248 mg, 0.304 mmol) was added. The reaction was stirred at 80 °C for 3.5 hours, and concentrated *in vacuo*. The residue was dissolved in DCM (50 mL). The resulted mixture was filtered through a pad of CELITE®, and the filtrate was washed with water (25 mL x 3) and brine (35 mL). The separated organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as yellow oil (395 mg, 70%).

MS (ESI, pos. ion) *m/z*: 397.0 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.36 (d, *J* = 1.59 Hz, 1H), 8.05 (d, *J* = 1.59 Hz, 1H), 6.94 (br s, 1H), 4.04 (s, 3H), 3.85 (q, *J* = 7.82 Hz, 2H), 1.33 (s, 12H).

Step 3) *N*-(5-(3-cyanopyrazolo[1,5-*a*]pyridin-5-yl)-2-methoxypyridin-3-yl)-2,2,2-trifluoroethanesulfonamide

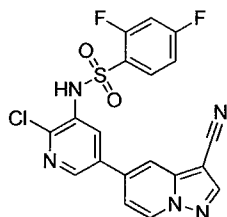
[216] To a solution of 5-bromopyrazolo[1,5-*a*]pyridine-3-carbonitrile (100 mg, 0.450 mmol) in 1,4-dioxane (20 mL) and water (4 mL) were added 2,2,2-trifluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)ethanesulfonamide (196 mg, 0.495 mmol), KOAc (88 mg, 0.900 mmol) and Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (74 mg, 0.09 mmol) under N<sub>2</sub> atmosphere. The reaction was stirred at 90 °C for 2.5 hours under N<sub>2</sub> atmosphere, then cooled to rt and stirred overnight. The mixture was concentrated *in vacuo*, then the residue was diluted with EtOAc (35 mL), and the resulted mixture was filtered through a pad of CELITE®. The filter cake was washed with EtOAc (35 mL) and the filtrate was washed with H<sub>2</sub>O (15 mL) and brine (20 mL). The separated organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2.5/1) to give the title compound as a yellow solid (94 mg, 51%).

MS (ESI, pos. ion) *m/z*: 412.0 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 10.15 (s, 1H), 9.03 (d, *J* = 7.32 Hz, 1H), 8.67 (s, 1H),

8.65 (d,  $J = 2.25$  Hz, 1H), 8.24 (d,  $J = 1.05$  Hz, 1H), 8.18 (d,  $J = 2.28$  Hz, 1H), 7.59 (dd,  $J = 1.80$ , 7.26 Hz, 1H), 4.63 (q,  $J = 9.78$  Hz, 2H), 4.00 (s, 3H).

Example 11 *N*-(2-chloro-5-(3-cyanopyrazolo[1,5-*a*]pyridin-5-yl)pyridin-3-yl)-2,4-difluorobenzenesulfonamide



[217] To a solution of 5-bromopyrazolo[1,5-*a*]pyridine-3-carbonitrile (110 mg, 0.5 mmol) in 1,4-dioxane (20 mL) were added *N*-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-2,4-difluorobenzenesulfonamide (235 mg, 0.55 mmol), KOAc (98 mg, 1 mmol), H<sub>2</sub>O (2 mL) and Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (81 mg, 0.1 mmol). The reaction was stirred at 93 °C under N<sub>2</sub> atmosphere for 2 hours, then concentrated *in vacuo*, and the residue was extracted with EtOAc (20 mL x 3). The combined organic phases were dried anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4.5/1) to give the title compound as a white solid (130 mg, 59%).

MS (ESI, pos. ion)  $m/z$ : 446.0 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 10.98 (br s, 1H), 9.08 (d,  $J = 7.29$  Hz, 1H), 8.87 (d,  $J = 2.67$  Hz, 1H), 8.71 (s, 1H), 8.41-8.39 (m, 2H), 7.84-7.76 (m, 1H), 7.63-7.54 (m, 2H), 7.26-7.20 (m, 1H).

#### BIOLOGICAL TESTING

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

[219] 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    |

[220] An Agilent XDB-C18, 2.1 x 30 mm, 3.5  $\mu$ M column was used for the analysis. 5  $\mu$ 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                       |

[221] 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  $\mu$ 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  $\mu$ L of the samples were injected.

| Example # | Human                     |                                  | Rat                       |                                  |
|-----------|---------------------------|----------------------------------|---------------------------|----------------------------------|
|           | T <sub>1/2</sub><br>(min) | CL <sub>int</sub><br>(mL/min/kg) | T <sub>1/2</sub><br>(min) | CL <sub>int</sub><br>(mL/min/kg) |
| Ex. 1     | 710.7                     | 2.45                             | 175.4                     | 14.16                            |
| Ex. 2     | ∞                         | N/A                              | ∞                         | N/A                              |
| Ex. 3     | 2404                      | 0.72                             | 575.1                     | 4.32                             |
| Ex. 4     | 299.2                     | 5.81                             | 153.3                     | 16.20                            |
| Ex. 5     | 303.0                     | 5.74                             | 216.7                     | 11.46                            |
| Ex. 6     | ∞                         | N/A                              | ∞                         | N/A                              |
| Ex. 7     | 3344                      | 0.52                             | 92.42                     | 26.87                            |
| Ex. 8     | 7825                      | 0.22                             | 1262                      | 1.97                             |
| Ex. 10    | 1223                      | 2.03                             | ∞                         | N/A                              |

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

[227] The compounds disclosed herein are assessed in pharmacokinetic studies in mice, rats, dogs or monkeys. The compounds are administered as a water solution, 2% HPMC + 1% TWEEN<sup>®</sup>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 and stored at -20 °C or -70 °C until analyzed by LC/MS/MS as described above.

Table 3 Pharmacokinetic profiles in rats

| Example # | iv dosing       |                         |                                  |                  |                           | F (%)  |
|-----------|-----------------|-------------------------|----------------------------------|------------------|---------------------------|--------|
|           | dose<br>(mg/kg) | T <sub>1/2</sub><br>(h) | AUC <sub>last</sub><br>(ng.h/mL) | Cl/F<br>(L/h/kg) | V <sub>ss</sub><br>(L/kg) |        |
| Ex. 1     | 2               | 3.93                    | 12121                            | 0.17             | 0.32                      | 102.00 |
| Ex. 2     | 2               | 3.70                    | 7720                             | 0.26             | 0.80                      | 69.48  |
| Ex. 3     | 2               | 2.77                    | 7069                             | 0.29             | 0.85                      | 94.75  |
| Ex. 4     | 2               | 1.93                    | 7353                             | 0.28             | 0.48                      | 91.75  |

|               |   |       |       |      |      |        |
|---------------|---|-------|-------|------|------|--------|
| <b>Ex. 5</b>  | 2 | 3.00  | 35176 | 0.05 | 0.20 | 96.20  |
| <b>Ex. 6</b>  | 1 | 10.96 | 40869 | 0.02 | 0.24 | 50.80  |
| <b>Ex. 7</b>  | 1 | 3.94  | 5328  | 0.19 | 0.63 | 80.10  |
| <b>Ex. 8</b>  | 1 | 10.77 | 41751 | 0.02 | 0.28 | 103.40 |
| <b>Ex. 10</b> | 1 | 2.74  | 1240  | 0.76 | 1.72 | 112.95 |

Table 4 Pharmacokinetic profiles in Mice, Dogs and Monkeys

| Example #    | Species | iv dosing    |                      |                               |               |                        | F (%) |
|--------------|---------|--------------|----------------------|-------------------------------|---------------|------------------------|-------|
|              |         | dose (mg/kg) | T <sub>1/2</sub> (h) | AUC <sub>last</sub> (ng.h/mL) | Cl/F (L/h/kg) | V <sub>ss</sub> (L/kg) |       |
| <b>Ex. 3</b> | Mouse   | 1            | 5.45                 | 57059                         | 0.02          | 0.13                   | 79.3  |
|              | Dog     | 1            | 0.67                 | 3672                          | 0.27          | 0.23                   | 108.5 |
|              | Monkey  | 1            | 9.70                 | 5978                          | 0.16          | 0.92                   | 59.8  |
| <b>Ex. 4</b> | Mouse   | 1            | 1.11                 | 5812                          | 0.17          | 0.18                   | 70.0  |
|              | Dog     | 1            | 6.13                 | 9069                          | 0.11          | 0.19                   | 108.5 |
|              | Monkey  | 1            | 4.64                 | 5739                          | 0.18          | 0.42                   | 24.0  |

#### Example C: Kinase Activity Assay

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

#### General Description for Kinase Assays

[229] Kinase assays can be performed by measurement of incorporation of  $\gamma$ -<sup>33</sup>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  $\mu$ L/well of 20  $\mu$ 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 3x with 100  $\mu$ L TBS. Kinase reactions are carried out in a total volume of 34  $\mu$ L in kinase buffer (5 mM Hepes pH 7.6, 15 mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10 mM MgCl<sub>2</sub>, 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  $\gamma$ - $^{33}\text{P}$  ATP is added to start the reaction ( $2 \times 10^6$  cpm of  $\gamma$ - $^{33}\text{P}$  ATP per well (3000 Ci/mmol) and 10  $\mu\text{M}$  unlabeled ATP, typically. The reactions are carried out for 1 hour at rt with shaking. Plates are washed 7x with TBS, followed by the addition of 50  $\mu\text{L}$ /well scintillation fluid (Wallac). Plates are read using a Wallac Trilux counter. This is only one format of such assays; various other formats are possible, as known to one skilled in the art.

[230] The above assay procedure can be used to determine the  $\text{IC}_{50}$  for inhibition and/or the inhibition constant,  $K_i$ . The  $\text{IC}_{50}$  is defined as the concentration of compound required to reduce the enzyme activity by 50% under the condition of the assay. The  $\text{IC}_{50}$  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  $\mu\text{M}$ , 3  $\mu\text{M}$ , 1  $\mu\text{M}$ , 0.3  $\mu\text{M}$ , 0.1  $\mu\text{M}$ , 0.03  $\mu\text{M}$ , 0.01  $\mu\text{M}$ , 0.003  $\mu\text{M}$ , 0.001  $\mu\text{M}$  and 0  $\mu\text{M}$ ).

#### PI3 KINASE GENERAL ASSAY PROTOCOL

##### PI3K (p110 $\alpha$ /p85 $\alpha$ ) (h) [Non-radioactive assay]

[231] PI3K (p110 $\alpha$ /p85 $\alpha$ ) (h) is incubated in assay buffer containing 10  $\mu\text{M}$  phosphatidylinositol 4,5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the ATP solution. After incubation for 30 minutes at room temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains europium-labelled anti-GST monoclonal antibody, GST-tagged GRP1 PH domain and streptavidin allophycocyanin. The plate is then read in time-resolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula  $\text{HTRF} = 10000 \times (\text{Em}665\text{nm}/\text{Em}620\text{nm})$ .

##### PI3K (p110 $\beta$ /p85 $\alpha$ ) (h) [Non-radioactive assay]

[232] PI3K (p110 $\beta$ /p85 $\alpha$ ) (h) is incubated in assay buffer containing 10  $\mu\text{M}$  phosphatidylinositol-4, 5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 30 minutes at room temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains

addition of 3% phosphoric acid solution. Aliquote of the reaction (10  $\mu$ L) 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.

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

[237] The compounds disclosed herein exhibited potent activities in the PI3K $\alpha$  (h) and mTOR (h) assays. Table 5 listed the IC<sub>50</sub>s of some examples described herein in the PI3K $\alpha$  (h) and mTOR (h) assays.

Table 5 Kinase inhibition data

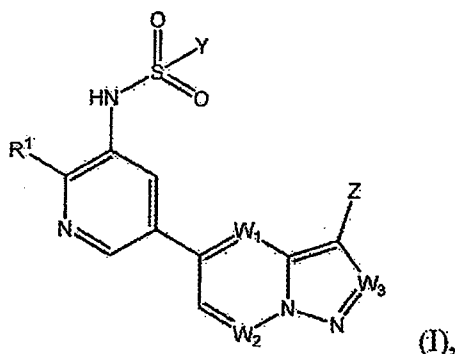
| Example # | IC <sub>50</sub> (nM) |                             |                            |                             |               |
|-----------|-----------------------|-----------------------------|----------------------------|-----------------------------|---------------|
|           | mTOR                  | PI3K                        |                            |                             |               |
|           |                       | p110 $\alpha$ /p85 $\alpha$ | p110 $\beta$ /p85 $\alpha$ | p110 $\delta$ /p85 $\alpha$ | p120 $\gamma$ |
| Ex. 1     | 9                     | 4                           | 84                         | 5                           | 6             |
| Ex. 2     | 4                     | 4                           | 45                         | 5                           | 5             |
| Ex. 3     | 4                     | 4                           | 41                         | 2                           | 6             |
| Ex. 4     | 4                     | 1                           | 22                         | 1                           | 15            |
| Ex. 5     | 7                     | 3                           | 75                         | 1                           | 6             |

[238] 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.

[239] 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

## WHAT IS CLAIMED IS:

1. A compound having Formula (I):



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

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

$Z$  is D, CN,  $N_3$ , or  $\text{---}X$ ;

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

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

-(C<sub>1</sub>-C<sub>4</sub>)alkylene-CN, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-OR<sup>a</sup>, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-NR<sup>a</sup>R<sup>b</sup>, (C<sub>6</sub>-C<sub>10</sub>)aryl, and 5-10 membered heteroaryl;

R<sup>i</sup> is H, D, Cl, OR<sup>a</sup>, NR<sup>a</sup>R<sup>b</sup>, (C<sub>1</sub>-C<sub>6</sub>)aliphatic, or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, wherein each of the (C<sub>1</sub>-C<sub>6</sub>)aliphatic and (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N<sub>3</sub>, OR<sup>a</sup>, SR<sup>a</sup>, and NR<sup>a</sup>R<sup>b</sup>;

each R<sup>a</sup> and R<sup>b</sup> is independently H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>6</sub>-C<sub>10</sub>)aryl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(5-10 membered heteroaryl), or R<sup>a</sup> and R<sup>b</sup> are taken together with the nitrogen atom to which they are attached form a 3-8 membered heterocyclic ring, wherein each of the above substituents is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N<sub>3</sub>, OH, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and (C<sub>1</sub>-C<sub>6</sub>)alkylamino; and

each R<sup>c</sup> is independently H, D, F, Cl, Br, I, N<sub>3</sub>, CN, OH, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, (C<sub>6</sub>-C<sub>10</sub>)aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N<sub>3</sub>, OH, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)haloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and (C<sub>1</sub>-C<sub>6</sub>)alkylamino.

2. The compound according to claim 1, wherein W<sub>1</sub> is N or CR<sup>c</sup>; and each of W<sub>2</sub> and W<sub>3</sub> is independently CR<sup>c</sup>.

3. The compound according to claim 1 or claim 2, wherein Z is CN, N<sub>3</sub>, or  $\frac{1}{2}-\equiv-X$ .

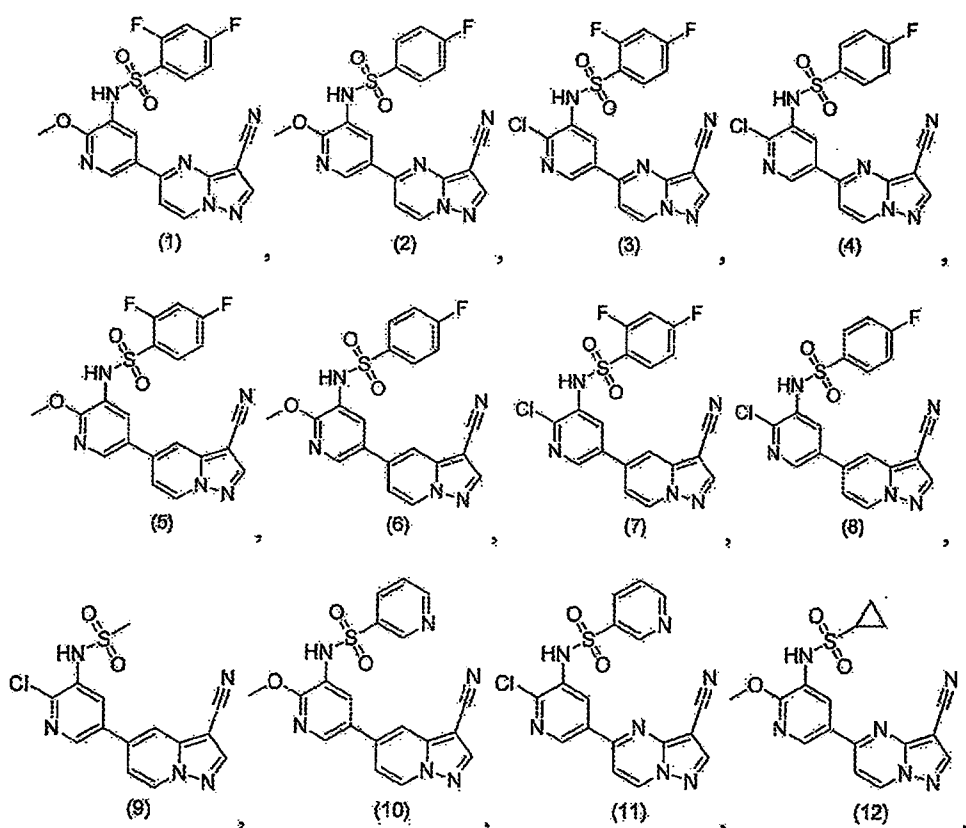
4. The compound according to any one of claims 1-3, wherein X is H, D, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, or -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, wherein each of the (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl and -(C<sub>1</sub>-C<sub>4</sub>)alkylene-(C<sub>3</sub>-C<sub>6</sub>)heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N<sub>3</sub>, OR<sup>a</sup>, SR<sup>a</sup>, NR<sup>a</sup>R<sup>b</sup>, -C(=O)NR<sup>a</sup>R<sup>b</sup>, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)haloalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, and (C<sub>2</sub>-C<sub>4</sub>)alkynyl.

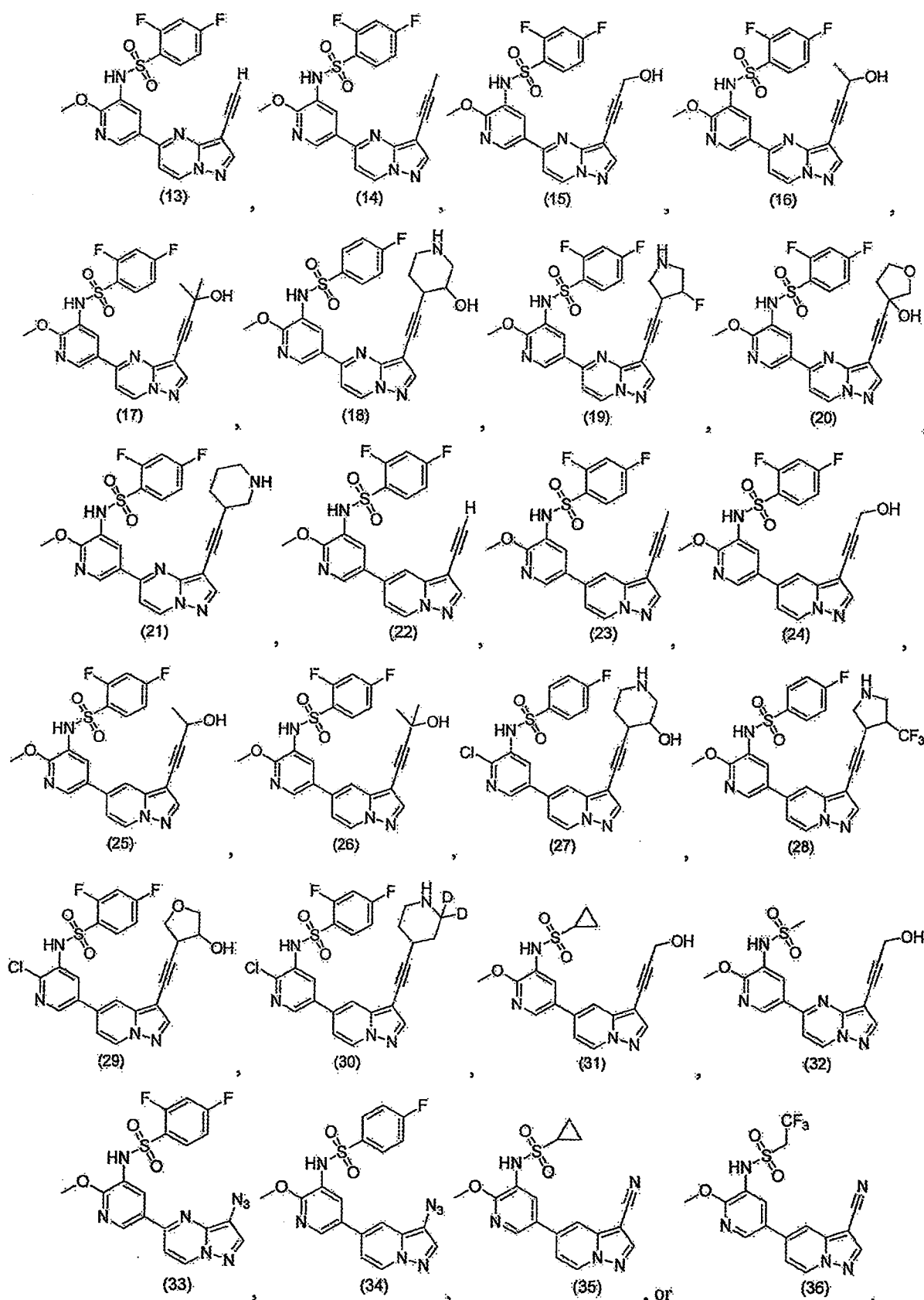
5. The compound according to any one of claims 1-4, wherein Y is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>6</sub>-C<sub>10</sub>)aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N<sub>3</sub>, OR<sup>a</sup>, SR<sup>a</sup>, NR<sup>a</sup>R<sup>b</sup>, -C(=O)NR<sup>a</sup>R<sup>b</sup>, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)haloalkyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, and 5-10 membered heteroaryl.

6. The compound according to any one of claims 1-5, wherein R<sup>1</sup> is H, D, Cl, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CF<sub>3</sub>, CH<sub>2</sub>CF<sub>3</sub>, OCH<sub>3</sub>, or OCH<sub>2</sub>CH<sub>3</sub>.

7. The compound according to any one of claims 1-6, wherein each R<sup>c</sup> is independently H, D, F, Cl, N<sub>3</sub>, CN, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkylamino, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, or (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl, wherein each of the (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkylamino, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl and (C<sub>3</sub>-C<sub>6</sub>)heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, CN, N<sub>3</sub>, OH, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, and (C<sub>1</sub>-C<sub>3</sub>)haloalkyl.

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





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

combination thereof.

10. The pharmaceutical composition according to claim 9 further comprising an additional therapeutic agent selected from a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis or a combination thereof.

11. The pharmaceutical composition according to claim 10, wherein the additional therapeutic agent is chlorambucil, melphalan, cyclophosphamide, ifosfamide, busulfan, carmustine, lomustine, streptozocin, cisplatin, carboplatin, oxaliplatin, dacarbazine, temozolomide, procarbazine, methotrexate, fluorouracil, cytarabine, gemcitabine, mercaptopurine, fludarabine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, topotecan, irinotecan, etoposide, trabectedin, dactinomycin, doxorubicin, epirubicin, daunorubicin, mitoxantrone, bleomycin, mitomycin, ixabepilone, tamoxifen, flutamide, gonadorelin analogues, megestrol, prednidone, dexamethasone, methylprednisolone, thalidomide, interferon alpha, leucovorin, sirolimus, temsirolimus, everolimus, afatinib, alisertib, amuvatinib, apatinib, axitinib, bortezomib, bosutinib, brivanib, cabozantinib, cediranib, crenolanib, crizotinib, dabrafenib, dacomitinib, danusertib, dasatinib, dovitinib, erlotinib, foretinib, ganetespib, gefitinib, ibrutinib, icotinib, imatinib, iniparib, lapatinib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, nilotinib, niraparib, oprozomib, olaparib, pazopanib, pictilisib, ponatinib, quizartinib, regorafenib, rigosertib, rucaparib, ruxolitinib, saracatinib, saridegib, sorafenib, sunitinib, tasocitinib, telatinib, tivantinib, tivozanib, tofacitinib, trametinib, vandetanib, veliparib, vemurafenib, vismodegib, volasertib, alemtuzumab, bevacizumab, brentuximab vedotin, catumaxomab, cetuximab, denosumab, gemtuzumab, ipilimumab, nimotuzumab, ofatumumab, panitumumab, ramucirumab, rituximab, tositumomab, trastuzumab, or a combination thereof.

12. Use of a compound according to any one of claims 1 to 8, or a pharmaceutical composition according to any one of claims 9 to 11 in the manufacture of a medicament for preventing, managing, treating or lessening the severity of a proliferative disorder, wherein the proliferative disorder is modulated by PI3K, mTOR, or a combination thereof.

13. The use according to claim 12, wherein the proliferative disorder is colon cancer, breast cancer, kidney cancer, lung cancer, prostate cancer or glioblastoma.

14. A method of inhibiting or modulating the activity of a protein kinase in a biological sample comprising contacting the biological sample with a compound according to any one of claims 1 to 8, or a pharmaceutical composition according to any one of claims 9 to 11, wherein the protein kinase is PI3K, mTOR, or a combination thereof.

15. Use of a compound according to any one of claims 1 to 8, or a pharmaceutical composition according to any one of claims 9 to 11 in the manufacture of a medicament for inhibiting or modulating the activity of a protein kinase, wherein the protein kinase is PI3K, mTOR, or a combination thereof.