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(54) Title: PYRIDOSULFONAMIDE DERIVATIVES AS PI3 KINASE INHIBITORS

(57) Abstract: Invented is a method of inhibiting the activity/function of PB kinases using pyridosulfonamide derivatives. Also invented is a method of treating one or more disease states selected from: autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries by the administration of pyridosulfonamide derivatives.

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PYRIDOSULFONAMIDE DERIVATIVES AS PI3 KINASE INHIBITORS

Field of the invention

This invention relates to the use of pyridosulfonamide derivatives for the modulation, notably the inhibition of the activity or function of the phosphoinositide 3' OH kinase family (hereinafter PI3 kinases), suitably, PI3Kα, PI3Kδ, PI3Kβ, or PI3Kγ. Suitably, the present invention relates to the use of pyridosulfonamides in the treatment of one or more disease states selected from: autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries.

Background of the invention

Cellular membranes represent a large store of second messengers that can be enlisted in a variety of signal transduction pathways. In regards function and regulation of effector enzymes in phospholipids signaling pathways, these enzymes generate second messengers from the membrane phospholipid pools (class I PI3 kinases (e.g. PI3Kalpha) are dual-specificity kinase enzymes, meaning they display both: lipid kinase (phosphorylation of phosphoinositides) as well as protein kinase activity, shown to be capable of phosphorylation of protein as substrate, including auto-phosphorylation as intramolecular regulatory mechanism. These enzymes of phospholipids signaling are activated in response to a variety of extra-cellular signals such as growth factors, mitogens, integrins (cell-cell interactions) hormones, cytokines, viruses and neurotransmitters such as described in Scheme I hereinafter and also by intracellular regulation by other signaling molecules (cross-talk, where the original signal can activate some parallel pathways that in a second step transmit signals to PI3Ks by intra-cellular signaling events), such as small GTPases, kinases or phosphatases for example. Intracellular regulation can also occur as a result of aberrant expression or lack of expression of cellular oncogenes or tumor suppressors. The inositol phospholipid (phosphoinositides) intracellular signaling pathways begin with activation of signaling molecules (extra cellular

ligands, stimuli, receptor dimerization, transactivation by heterologous receptor (e.g. receptor tyrosine kinase) and the recruitment and activation of PI3K including the involvement of G-protein linked transmembrane receptor integrated into the plasma membrane.

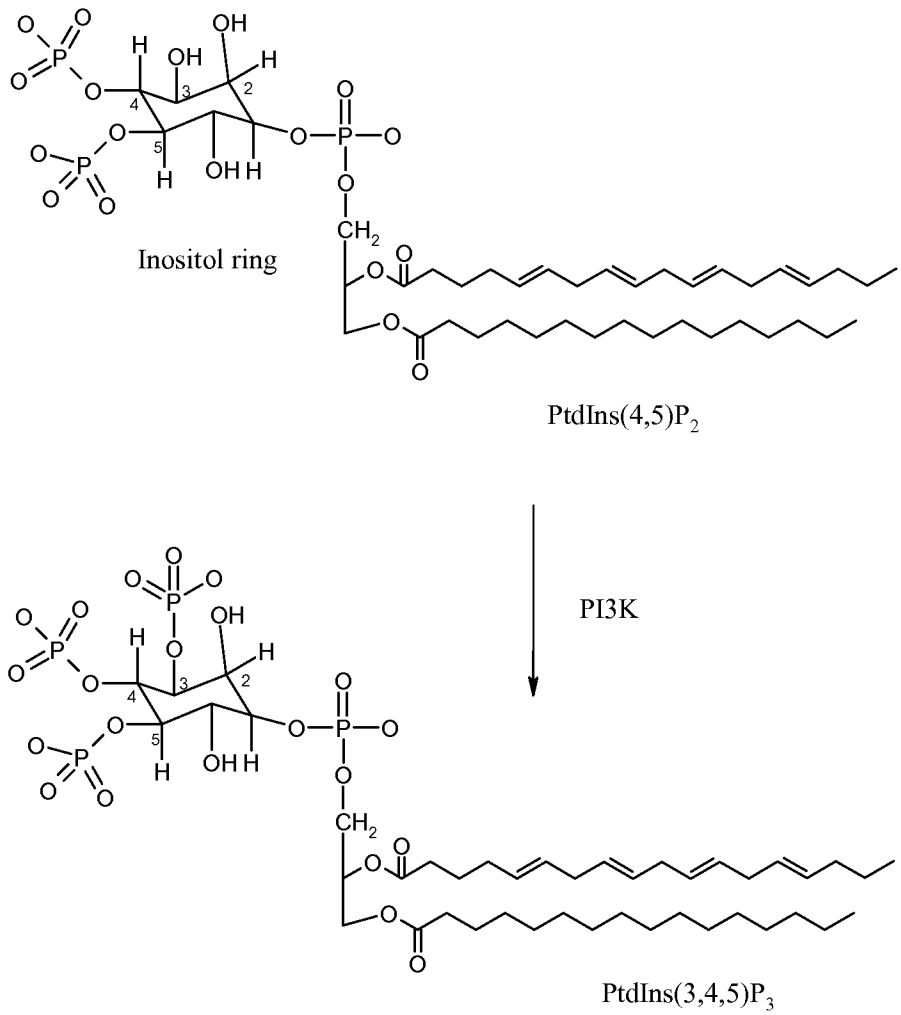
PI3K converts the membrane phospholipid $PI(4,5)P_2$ into $PI(3,4,5)P_3$ that functions as a second messenger. PI and PI(4)P are also substrates of PI3K and can be phosphorylated and converted into PI3P and $PI(3,4)P_2$, respectively. In addition, these phosphoinositides can be converted into other phosphoinositides by 5'–specific and 3'-specific phophatases, thus PI3K enzymatic activity results either directly or indirectly in the generation of two 3' –phosphoinositide subtypes that function as 2nd messengers in intra-cellular signal transduction pathways (Trends Biochem. Sci. 22(7) p.267-72 (1997) by Vanhaesebroeck et al.: Chem. Rev. 101(8) p.2365-80 (2001) by Leslie et al (2001); Annu. Rev. Cell.Dev. Biol. 17p, 615-75 (2001) by Katso et al. and Cell. Mol. Life Sci. 59(5) p.761-79 (2002) by Toker et al.). Multiple PI3K isoforms categorized by their catalytic subunits, their regulation by corresponding regulatory subunits, expression patterns and signaling-specific functions (p110α, β, δ and γ) perform this enzymatic reaction (Exp. Cell. Res. 25 (1) p. 239-54 (1999) by Vanhaesebroeck and Katso et al., 2001, above).

The closely related isoforms p110α and β are ubiquitously expressed, while δ and γ are more specifically expressed in the haematopoietic cell system, smooth muscle cells, myocytes and endothelial cells (Trends Biochem. Sci. 22(7) p.267-72 (1997) by Vanhaesebroeck et al.). Their expression might also be regulated in an inducible manner depending on the cellular, tissue type and stimuli as well as disease context. Inducibility of protein expression includes synthesis of protein as well as protein stabilization that is in part regulated by association with regulatory subunits.

To date, eight mammalian PI3Ks have been identified, divided into three main classes (I, II, and III) on the basis of sequence homology, structure, binding partners, mode of activation, and substrate preference. In vitro, class I PI3Ks can phosphorylate phosphatidylinositol (PI), phosphatidylinositol-4-phosphate (PI4P), and phosphatidylinositol-4,5-bisphosphate ($PI(4,5)P_2$) to produce phosphatidylinositol-3-phosphate (PI3P), phosphatidylinositol-3,4-bisphosphate ($PI(3,4)P_2$, and phosphatidylinositol-3,4,5-trisphosphate ($PI(3,4,5)P_3$,

respectively. Class II PI3Ks phosphorylate PI and phosphatidylinositol-4-phosphate. Class III PI3Ks can only phosphorylate PI (Vanhaesebrokeck et al., 1997, above; Vanhaesebroeck et al., 1999, above and Leslie et al, 2001, above)

Scheme I: Conversion of PI(4,5)P2 to PIP3



As illustrated in Scheme I above, phosphoinositide 3-kinases (PI3Ks) phosphorylate the hydroxyl of the third carbon of the inositol ring. The phosphorylation of phosphoinositides that generate PtdIns to 3,4,5-trisphosphate (PtdIns(3,4,5)P_3), PtdIns(3,4)P_2 and PtdIns(3)P produce second messengers for a variety of signal transduction pathways, including those essential to cell proliferation, cell differentiation, cell growth, cell size, cell survival, apoptosis, adhesion, cell motility, cell migration, chemotaxis, invasion, cytoskeletal rearrangement, cell shape changes, vesicle trafficking and metabolic pathway

(Katso et al., 2001, above and Mol. Med. Today 6(9) p. 347-57 (2000) by Stein). G-protein coupled receptors mediate phosphoinositide 3'OH-kinase activation via small GTPases such as Gβγ and Ras, and consequently PI3K signaling plays a central role in establishing and coordinating cell polarity and dynamic organization of the cytoskeleton – which together provides the driving force of cells to move.

Chemotaxis – the directed movement of cells toward a concentration gradient of chemical attractants, also called chemokines is involved in many important diseases such as inflammation/auto-immunity, neurodegeneration, antiogenesis, invasion/metastasis and wound healing (Immunol. Today 21(6) p. 260-4 (2000) by Wyman et al.; Science 287(5455) p. 1049-53 (2000) by Hirsch et al.; FASEB J. 15(11) p. 2019-21 (2001) by Hirsch et al. and Nat. Immunol. 2(2) p. 108-15 (2001) by Gerard et al.).

Advances using genetic approaches and pharmacological tools have provided insights into signalling and molecular pathways that mediate chemotaxis in response to chemoattractant activated G-protein coupled receptors. PI3-Kinase, responsible for generating these phosphorylated signalling products, was originally identified as an activity associated with viral oncoproteins and growth factor receptor tyrosine kinases that phosphorylates phosphatidylinositol (PI) and its phosphorylated derivatives at the 3'-hydroxyl of the inositol ring (Panayotou et al., Trends Cell Biol. 2 p. 358-60 (1992)). However, more recent biochemical studies revealed that class I PI3 kinases (e.g. class IB isoform PI3Kγ) are dual-specific kinase enzymes, meaning they display both lipid kinase and protein kinase activity, shown to be capable of phosphorylation of other proteins as substrates, as well as auto-phosphorylation as an intra-molecular regulatory mechanism.

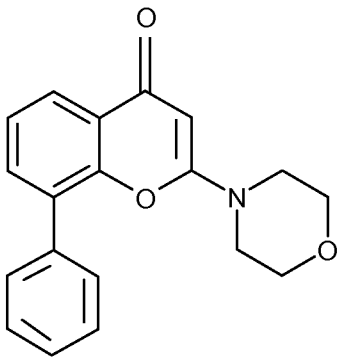
PI3-kinase activation, is therefore believed to be involved in a range of cellular responses including cell growth, differentiation, and apoptosis (Parker et al., Current Biology, 5 p. 577-99 (1995); Yao et al., Science, 267 p. 2003-05 (1995)). PI3-kinase appears to be involved in a number of aspects of leukocyte activation. A p85-associated PI3-kinase activity has been shown to physically associate with the cytoplasmic domain of CD28, which is an important costimulatory molecule for the activation of T-cells in response to antigen (Pages et al., Nature, 369 p. 327-29 (1994); Rudd, Immunity 4 p. 527-34

(1996)). Activation of T cells through CD28 lowers the threshold for activation by antigen and increases the magnitude and duration of the proliferative response. These effects are linked to increases in the transcription of a number of genes including interleukin-2 (IL2), an important T cell growth factor (Fraser et al., Science 251 p. 313-16 (1991)). Mutation of CD28 such that it can no longer interact with PI3-kinase leads to a failure to initiate IL2 production, suggesting a critical role for PI3-kinase in T cell activation. PI3Kγ has been identified as a mediator of G beta-gamma-dependent regulation of JNK activity, and G beta-gamma are subunits of heterotrimeric G proteins (Lopez-Ilasaca et al., J. Biol. Chem. 273(5) p. 2505-8 (1998)). Cellular processes in which PI3Ks play an essential role include suppression of apoptosis, reorganization of the actin skeleton, cardiac myocyte growth, glycogen synthase stimulation by insulin, TNFα-mediated neutrophil priming and superoxide generation, and leukocyte migration and adhesion to endothelial cells.

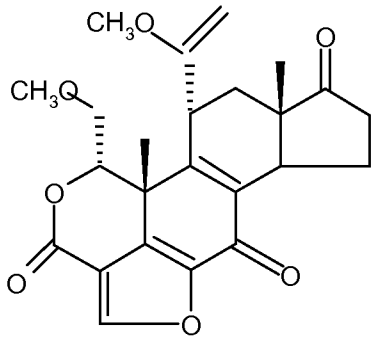
Recently, (Laffargue et al., Immunity 16(3) p. 441-51 (2002)) it has been described that PI3Kγ relays inflammatory signals through various G(i)-coupled receptors and its central to mast cell function, stimuli in context of leukocytes, immunology includes cytokines, chemokines, adenosines, antibodies, integrins, aggregation factors, growth factors, viruses or hormones for example (J. Cell. Sci. 114(Pt 16) p. 2903-10 (2001) by Lawlor et al.; Laffargue et al., 2002, above and Curr. Opinion Cell Biol. 14(2) p. 203-13 (2002) by Stephens et al.).

Specific inhibitors against individual members of a family of enzymes provide invaluable tools for deciphering functions of each enzyme. Two compounds, LY294002 and wortmannin (cf. hereinafter), have been widely used as PI3-kinase inhibitors. These compounds are non-specific PI3K inhibitors, as they do not distinguish among the four members of Class I PI3-kinases. For example, the IC_{50} values of wortmannin against each of the various Class I PI3-kinases are in the range of 1-10 nM. Similarly, the IC_{50} values for LY294002 against each of these PI3-kinases is about 15-20 μM (Fruman et al., Ann. Rev. Biochem., 67, p. 481-507 (1998)), also 5-10 microM on CK2 protein kinase and some inhibitory activity on phospholipases. Wortmannin is a fungal metabolite which irreversibly inhibits PI3K activity by binding covalently to the catalytic domain of this enzyme. Inhibition of PI3K activity by wortmannin eliminates subsequent cellular response to the extracellular factor. For example, neutrophils respond to the chemokine fMet-Leu-Phe (fMLP) by stimulating

PI3K and synthesizing PtdIns (3, 4, 5)P_3. This synthesis correlates with activation of the respirators burst involved in neutrophil destruction of invading microorganisms. Treatment of neutrophils with wortmannin prevents the fMLP-induced respiratory burst response (Thelen et al., Proc. Natl. Acad. Sci. USA, 91, p. 4960-64 (1994)). Indeed, these experiments with wortmannin, as well as other experimental evidence, shows that PI3K activity in cells of hematopoietic lineage, particularly neutrophils, monocytes, and other types of leukocytes, is involved in many of the non-memory immune response associated with acute and chronic inflammation.



LY294002



Wortmannin

Based on studies using wortmannin, there is evidence that PI3-kinase function is also required for some aspects of leukocyte signaling through G-protein coupled receptors (Thelen et al., 1994, above). Moreover, it has been shown that wortmannin and LY294002 block neutrophil migration and superoxide release. Cyclooxygenase inhibiting benzofuran derivatives are disclosed by John M. Janusz et al., in J. Med. Chem. 1998; Vol. 41, No. 18.

It is now well understood that deregulation of onocogenes and tumour-suppressor genes contributes to the formation of malignant tumours, for example by way of increase cell growth and proliferation or increased cell survival. It is also now known that signaling pathways mediated by the PI3K family have a central role in a number of cell processes including proliferation and survival, and deregulation of these pathways is a causative factor a wide spectrum of human cancers and other diseases (Katso *et al.*, Annual Rev. Cell Dev. Biol., 2001, 17: 615-617 and Foster *et al.*, J. Cell Science, 2003, 116: 3037-3040).

Class I PI3K is a heterodimer consisting of a p110 catalytic subunit and a regulatory subunit, and the family is further divided into class Ia and Class Ib enzymes on the basis of regulatory partners and mechanism of regulation. Class Ia enzymes consist of three distinct catalytic subunits (p110α, p110β, and p110δ) that dimerise with five distinct regulatory subunits (p85α, p55α, p50α, p85β, and p55γ), with all catalytic subunits being able to interact with all regulatory subunits to form a variety of heterodimers. Class Ia PI3K are generally activated in response to growth factor-stimulation of receptor tyrosine kinases, via interaction of the regulatory subunit SH2 domains with specific phospho-tyrosine residues of the activated receptor or adaptor proteins such as IRS-1. Small GTPases (ras as an example) are also involved in the activation of PI3K in conjunction with receptor tyrosine kinase activation. Both p110α and p110β are constitutively expressed in all cell types, whereas p110δ expression is more restricted to leukocyte populations and some epithelial cells. In contrast, the single Class Ib enzyme consists of a p110γ catalytic subunit that interacts with a p101 regulatory subunit. Furthermore, the Class Ib enzyme is activated in response to G-protein coupled receptor (GPCR) systems and its expression appears to be limited to leukocytes.

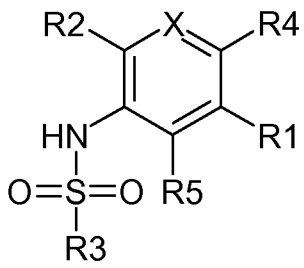
There is now considerable evidence indicating that Class Ia PI3K enzymes contribute to tumourigenesis in a wide variety of human cancers, either directly or indirectly (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501). For example, the p110α subunit is amplified in some tumours such as those of the ovary (Shayesteh, *et al.*, Nature Genetics, 1999, 21: 99-102) and cervix (Ma *et al.*, Oncogene, 2000, 19: 2739-2744). More recently, activating mutations within p110α (PIK3CA gene) have been associated with various other tumors such as those of the colon and of the breast and lung (Samuels, et al., Science, 2004, 304, 554). Tumor-related mutations in p85α have also been identified in cancers such as those of the ovary and colon (Philp *et al.*, Cancer Research, 2001, 61, 7426-7429). In addition to direct effects, it is believed that activation of Class Ia PI3K contributes to tumourigenic events that occur upstream in signaling pathways, for example by way of ligand-dependent or ligand-independent activation of receptor tyrosine kinases, GPCR systems or integrins (Vara *et al.*, Cancer Treatment Reviews, 2004, 30, 193-204). Examples of such upstream signaling pathways include over-expression of the receptor tyrosine kinase Erb2 in a variety of tumors leading to activation of PI3K-mediated pathways (Harari *et al.*, Oncogene, 2000, 19, 6102-6114) and over-expression of

the oncogene Ras (Kauffmann-Zeh *et al.*, Nature, 1997, 385, 544-548). In addition, Class Ia PI3Ks may contribute indirectly to tumourigenesis caused by various downstream signaling events. For example, loss of function of the PTEN tumor-suppressor phosphatase that catalyses conversion of PI(3,4,5)P3 back to PI(4,5)P2 is associated with a very broad range of tumors via deregulation of PI3K-mediated production of PI(3,4,5)P3 (Simpson and Parsons, Exp. Cell Res., 2001, 264, 29-41). Furthermore, augmentation of the effects of other PI3K-mediated signaling events is believed to contribute to a variety of cancers, for example by activation of AKT (Nicholson and Andeson, Cellular Signaling, 2002, 14, 381-395).

In addition to a role in mediating proliferative and survival signaling in tumor cells, there is also good evidence that class Ia PI3K enzymes also contributes to tumourigenesis via its function in tumor-associated stromal cells. For examples, PI3K signaling is known to play an important role in mediating angiogenic events in endothelial cells in response to pro-angiogenic factors such as VEGF (abid *et al.*, Arterioscler, Thromb. Vasc. Biol., 2004, 24, 294-300). As Class I PI3K enzymes are also involved in motility and migration (Sawyer, Expert Opinion investing. Drugs, 2004, 13, 1-19), PI3K inhibitors are anticipated to provide therapeutic benefit via inhibition of tumor cell invasion and metastasis.

Summary of the Invention

This invention relates to method of treating cancer in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I):



(I)

, or a pharmaceutically acceptable salt thereof, in which

R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R2 is selected from the group consisting of: halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, alkoxy, nitro, acyloxy, and aryloxy;

R3, R4 and R5 are independently selected from the group consisting of: hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, hydroxyl, alkoxy, nitro, acyloxy, and aryloxy;

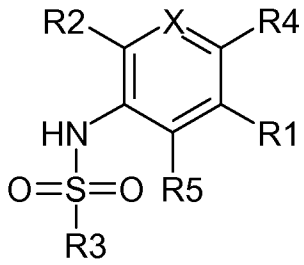
X is N or C;

provided that R1 is not a substituted quinolinyl, substituted quinoxalinyl, substituted quinazolinyl, substituted naphthyridinyl, pyridoprimidinyl, or substituted pyridoprimidinyl;

further provided that when X is C, R3 is an optionally substituted pyridine ring.

Detailed Description of the Invention

This invention also relates to novel compounds of Formula (I)(A):



(I)(A)

, or a pharmaceutically acceptable salt thereof, in which

R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R2 is selected from the group consisting of: halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, alkoxy, nitro, acyloxy, and aryloxy;

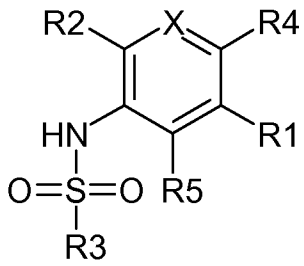
R3, R4 and R5 are independently selected from the group consisting of: hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, hydroxyl, alkoxy, nitro, acyloxy, and aryloxy;

X is N or C;

provided that R1 is not a thiazolyl, substituted thiazolyl, substituted quinolinyl, substituted quinoxalinyl, substituted quinazolinyl, substituted naphthyridinyl, pyridoprimidinyl, or substituted pyridoprimidinyl;

further provided that when X is C, R3 is an optionally substituted pyridine ring.

This invention relates novel compounds of Formula (I)(B):



(I)(B)

, or a pharmaceutically acceptable salt thereof, in which

R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, and substituted aryl;

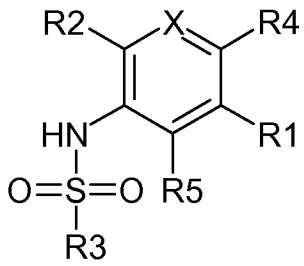
R2 is selected from the group consisting of: halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, alkoxy, nitro, acyloxy, and aryloxy;

R3, R4 and R5 are independently selected from the group consisting of: hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, hydroxyl, alkoxy, nitro, acyloxy, and aryloxy;

X is N or C;

provided that when X is C, R3 is an optionally substituted pyridine ring.

This invention relates novel compounds of Formula (I)(C):



(I)(C)

, or a pharmaceutically acceptable salt thereof, in which

R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, and substituted aryl;

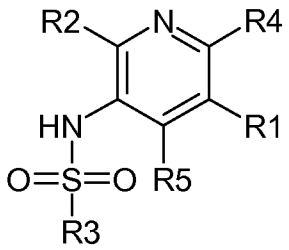
R2 is selected from the group consisting of: halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, alkoxy, nitro, acyloxy, and aryloxy;

R3 is selected from the group consisting of: hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, hydroxyl, alkoxy, nitro, acyloxy, and aryloxy;

R4 and R5 are each independently selected from the group consisting of: hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, cyano, alkoxy, nitro and acyloxy;

X is N.

This invention also relates to a compound of Formula (I)(D):



(I)(D)

, or a pharmaceutically acceptable salt thereof, in which

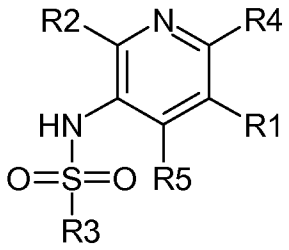
R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, unsubstituted heteroaryl, and substituted heteroaryl,

wherein the substituted heteroaryl is selected from the group consisting of: quinazolinonyl, tetrahydropyridoprimidinyl, pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl;

R2 is selected from the group consisting of: hydroxyl, aminocarbonyl, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, cyano, alkoxy, nitro and acyloxy; and

R3, R4 and R5 are independently selected from the group consisting of: hydroxyl, hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, alkoxy, nitro, acyloxy, and aryloxy.

This invention also relates to a compound represented by Formula (I)(E):



(I)(E)

, or a pharmaceutically acceptable salt thereof, in which

R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, unsubstituted heteroaryl, and substituted heteroaryl,

wherein the substituted heteroaryl is selected from the group consisting of: quinazolinonyl, tetrahydropyridoprimidinyl, pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl;

R2 is selected from the group consisting of: hydroxyl, aminocarbonyl, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, cyano, alkoxy, nitro and acyloxy;

R3 is selected from the group consisting of: hydroxyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, alkoxy, and aryloxy;

R4 and R5 are each independently selected from the group consisting of: hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, cyano, alkoxy, nitro and acyloxy.

This invention also relates to a compound of (I)(A)--(I)(E), wherein R1 is selected from the group consisting of: aryl, substituted aryl, unsubstituted heteroaryl, and substituted heteroaryl, wherein the substituted heteroaryl is

selected from the group consisting of: quinazolinonyl, tetrahydropyridoprimidinyl, pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl;

R2 is selected from: cyano, substitituted amino, halogen, C1-6alkyl, amino, alkoxy and cyclopropyl;

R3 is selected from the group consisting of: amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, alkoxy, and aryloxy; and

R4 and R5 are each independently selected from the group consisting of: hydrogen, halogen, acyl, amino, C1-6alkyl and cyclopropyl;
or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds according to any one of (I)(A)—(I)(E), wherein R1 is phenyl or substituted phenyl; or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds according to any one of (I)(A)—(I)(E), wherein R1 is unsubstituted heteroaryl or substituted heteroaryl, wherein the substituted heteroaryl is selected from the group consisting of: quinazolinonyl, tetrahydropyridoprimidinyl, pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl.

This invention also relates to compounds according to any one of (I)(A)—(I)(E), wherein R2 is alkoxy, C1-6alkyl, substituted C1-6alkyl, cyano, amino or halogen; or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds according to any one of (I)(A)—(I)(E), wherein R2 is methoxy, halogen, ethoxy, methyl, ethyl, trifluoromethyl, cyano or amino.

This invention also relates to compounds according to any one of (I)(A)—(I)(E), wherein R3 is aryl optionally substituted with one to three groups selected from: halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, alkoxy, and aryloxy, wherein two adjacent substituents may form an additional 5 or 6-membered non-aromatic ring containing zero to three heteroatoms; or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds according to any one of (I)(A)—(I)(E), wherein R4 and R5 are each independently selected from the group consisting of: hydrogen, halogen, cyano, amino, C1-6alkyl and cyclopropyl;

or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of treating cancer in a human in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I)(D) or (I)(E).

This invention also relates to the following compounds:

N-(2-chloro-5-phenyl-3-pyridinyl)benzenesulfonamide,
N-(6-chloro-3,4'-bipyridin-5-yl)benzenesulfonamide,
N-(6-chloro-3,3'-bipyridin-5-yl)benzenesulfonamide,
N-(4-{6-chloro-5-[(phenylsulfonyl)amino]-3-pyridinyl}phenyl)acetamide,
N-(3-{6-chloro-5-[(phenylsulfonyl)amino]-3-pyridinyl}phenyl)acetamide,
N-[5-(3-aminophenyl)-2-chloro-3-pyridinyl]benzenesulfonamide,

N-[5-(4-aminophenyl)-2-chloro-3-pyridinyl]benzenesulfonamide,
N-(2-chloro-5-{4-[(methylsulfonyl)amino]phenyl}-3-pyridinyl)benzenesulfonamide,
N-[2-chloro-5-(1*H*-indol-5-yl)-3-pyridinyl]benzenesulfonamide,
N-{2-chloro-5-[4-(trifluoromethyl)phenyl]-3-pyridinyl}benzenesulfonamide,
N-{2-chloro-5-[4-(methyloxy)phenyl]-3-pyridinyl}benzenesulfonamide,
N-{2-chloro-5-[3-(methyloxy)phenyl]-3-pyridinyl}benzenesulfonamide,
N-{2-chloro-5-[3-(trifluoromethyl)phenyl]-3-pyridinyl}benzenesulfonamide,
N-(6'-amino-6-chloro-3,3'-bipyridin-5-yl)benzenesulfonamide,
N-[6-chloro-6'-(dimethylamino)-3,3'-bipyridin-5-yl]benzenesulfonamide,
N-[6-chloro-6'-(4-morpholinyl)-3,3'-bipyridin-5-yl]benzenesulfonamide,
N-{2-chloro-5-[2-(methyloxy)-5-pyrimidinyl]-3-pyridinyl}benzenesulfonamide,
N-{5-[2,4-bis(methyloxy)-5-pyrimidinyl]-2-chloro-3-pyridinyl}benzenesulfonamide,
N-[2-chloro-5-(5-pyrimidinyl)-3-pyridinyl]benzenesulfonamide,
N-{2-chloro-5-[6-(methyloxy)-2-naphthalenyl]-3-pyridinyl}benzenesulfonamide,
N-[2-chloro-5-(1*H*-indol-6-yl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(1*H*-pyrazol-4-yl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(3-furanyl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(1-methyl-1*H*-pyrazol-4-yl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(3-thienyl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(3-quinolinyl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(2-naphthalenyl)-3-pyridinyl]benzenesulfonamide,
N-[5-(2-amino-5-pyrimidinyl)-2-chloro-3-pyridinyl]benzenesulfonamide,
N-{2-chloro-5-[2-(methylamino)-5-pyrimidinyl]-3-pyridinyl}benzenesulfonamide,
N-[2-chloro-5-(2-methyl-1,3-benzothiazol-5-yl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]benzenesulfonamide,
N-[5-(2-amino-6-methyl-4-pyrimidinyl)-2-chloro-3-pyridinyl]benzenesulfonamide,
N-(4-{6-chloro-5-[(phenylsulfonyl)amino]-3-pyridinyl}-6-methyl-2-pyrimidinyl)acetamide,
N-[5-(6-bromoimidazo[1,2-*a*]pyridin-3-yl)-2-chloro-3-pyridinyl]benzenesulfonamide,

N-(2-chloro-5-imidazo[1,2-*a*]pyridin-6-yl-3-pyridinyl)benzenesulfonamide,
N-[2-chloro-5-(2-phenyl-4-pyrimidinyl)-3-pyridinyl]benzenesulfonamide,
N-{2-chloro-5-[3-(3-pyridinyl)imidazo[1,2-*a*]pyridin-6-yl]-3-pyridinyl}benzenesulfonamide,
N-{2-chloro-5-[3-(4-pyridinyl)imidazo[1,2-*a*]pyridin-6-yl]-3-pyridinyl}benzenesulfonamide,
N-{5-[2-amino-4-(4-pyridinyl)-5-pyrimidinyl]-2-chloro-3-pyridinyl}benzenesulfonamide,
N-[2-chloro-5-(1-methyl-1*H*-imidazol-5-yl)-3-pyridinyl]benzenesulfonamide,
N-[5-(2-amino-4-pyrimidinyl)-2-chloro-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(2,6-diamino-4-pyrimidinyl)-3-pyridinyl]benzenesulfonamide,
N-{2-chloro-5-[3-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-*a*]pyridin-6-yl]-3-pyridinyl}benzenesulfonamide,
N-[2-chloro-5-(6-quinazolinyl)-3-pyridinyl]benzenesulfonamide,
N-{2-chloro-5-[3-oxo-4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]-3-pyridinyl}benzenesulfonamide,
N-(2-chloro-5-{4-[(4-chlorophenyl)methyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl}-3-pyridinyl)benzenesulfonamide,
N-{2-chloro-5-[4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]-3-pyridinyl}benzenesulfonamide,
N-{2-chloro-5-[3-oxo-4-(phenylmethyl)-3,4-dihydro-6-quinoxalinyl]-3-pyridinyl}benzenesulfonamide,
N-[2-chloro-5-(1-methyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)-3-pyridinyl]benzenesulfonamide,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-2-naphthalenesulfonamide,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-2,1,3-benzoxadiazole-4-sulfonamide,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-2-naphthalenesulfonamide,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-3,4-bis(methyloxy)-1,5-cyclohexadiene-1-sulfonamide,
N-[4-({[2-chloro-5-(6-quinolinyl)-3-pyridinyl]amino}sulfonyl)phenyl]acetamide,
4-({[2-chloro-5-(6-quinolinyl)-3-pyridinyl]amino}sulfonyl)benzoic acid,
3-({[2-chloro-5-(6-quinolinyl)-3-pyridinyl]amino}sulfonyl)benzoic acid,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-4-methyl-3,4,4a,8a-tetrahydro-2*H*-1,4-benzoxazine-7-sulfonamide,

N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-3,4-bis(methyloxy)benzenesulfonamide,
3-({[2-chloro-5-(6-quinolinyl)-3-pyridinyl]amino}sulfonyl)-4-(methyloxy)benzoic acid,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-3-(trifluoromethyl)benzenesulfonamide,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-4-(1,1-dimethylethyl)benzenesulfonamide,
N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-2-methyl-4-nitrobenzenesulfonamide,
Methyl 3-({[2-chloro-5-(6-quinolinyl)-3-pyridinyl]amino}sulfonyl)benzoate,
N-[2-(methyloxy)-5-(6-quinolinyl)-3-pyridinyl]methanesulfonamide,
N-[2-(ethyloxy)-5-(6-quinolinyl)-3-pyridinyl]benzenesulfonamide,
N-[2-methyl-5-(6-quinolinyl)-3-pyridinyl]methanesulfonamide,
N-[2-chloro-5-(4-oxo-1,4-dihydro-6-quinazolinyl)-3-pyridinyl]benzenesulfonamide,
2,4-difluoro-*N*-[2-(methyloxy)-5-(4-oxo-3-phenyl-3,4-dihydro-6-quinazolinyl)-3-pyridinyl]benzenesulfonamide and
N-{2-chloro-5-[4-(4-pyridinyl)-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-3-pyridinyl}benzenesulfonamide;
or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of treating one or more disease states selected from: autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection and lung injuries, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I).

Included in the present invention are methods of co-administering the present PI3 kinase inhibiting compounds with further active ingredients.

This invention also relates to a method of treating cancer, which comprises co-administering to a subject in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof; and at least one anti-neoplastic agent such as one selected from the group consisting of: anti-microtubule agents, plantinum coordination complexes, alkylating agents, antibiotic agents,

topoisomerase II inhibitors, antimetabolites, topoisomerase I hinibitors, hormones and hormonal anlogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

This invention also relates to a method of treating cancer, which comprises co-administering to a subject in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof; and at least one signal transduction pathway inhibitor such as one selected from the group consisting of: receptor tyrosine kinase inhibitor, non-receptor tyrosine kinase inhibitor, SH2/SH3 domain blocker, serine/threonine kinase inhibitor, phosphotidyl inositol-3 kinase inhibitor, myo-inositol singaling inhibitor, and Ras oncogene inhibitor.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term “therapeutically effective amount” means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention.

Definitions

By the term “substituted amino” as used herein, is meant –NR30R40 wherein each R30 and R40 is independently selected from a group including hydrogen, C1-6alkyl, acyl, C3-C7cycloalkyl, wherein at least one of R30 and R40 is not hydrogen.

By the term “aminocarbonyl” as used herein is meant –C(O)(amino) or –C(O)(substituted amino).

By the term "acyl" as used herein, unless otherwise defined, is meant –C(O)(alkyl), -C(O)(cycloalkyl).

By the term "aryl" as used herein, unless otherwise defined, is meant aromatic, hydrocarbon, ring system. The ring system may be monocyclic or fused polycyclic (e.g. bicyclic, tricyclic, etc.). In various embodiments, the monocyclic aryl ring is C5-C10, or C5-C7, or C5-C6, where these carbon numbers refer to the number of carbon atoms that form the ring system. A C6 ring system, i.e. a phenyl ring is a suitable aryl group. In various embodiments, the polycyclic ring is a bicyclic aryl group, where suitable bicyclic aryl groups are C8-C12, or C9-C10. A naphthyl ring, which has 10 carbon atoms, is a suitable polycyclic aryl group.

By the term "heteroaryl" as used herein, unless otherwise defined, is meant an aromatic ring system containing carbon(s) and at least one heteroatom. Heteroaryl may be monocyclic or polycyclic. A monocyclic heteroaryl group may have 1 to 4 heteroatoms in the ring, while a polycyclic heteroaryl may contain 1 to 10 hetero atoms. A polycyclic heteroaryl ring may contain fused, spiro or bridged ring junctions, for example, bicyclic heteroaryl is a polycyclic heteroaryl. Bicyclic heteroaryl rings may contain from 8 to 12 member atoms. Monocyclic heteroaryl rings may contain from 5 to 8 member atoms (carbons and heteroatoms). Exemplary heteroaryl groups include but are not limited to: benzofuran, benzothiophene, furan, imidazole, indole, isothiazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinoline, quinazoline, quinoxaline, thiazole, and thiophene.

By the term "monocyclic heteroaryl" as used herein, unless otherwise defined, is meant a monocyclic heteroaryl ring containing 1-5 carbon atoms and 1-4 hetero atoms.

By the term "alkylcarboxy" as used herein, unless otherwise defined, is meant $–(CH_2)_nCOOR_{80}$, wherein R80 is hydrogen or C1-C6alkyl, n is 0-6.

By the term "alkoxy" as used herein is meant –O(alkyl) including $-OCH_3$, $-OCH_2CH_3$ and $-OC(CH_3)_3$ where alkyl is as described herein.

By the term "alkylthio" as used herein is meant –S(alkyl) including $-SCH_3$, $-SCH_2CH_3$ where where alkyl is as described herein.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C_3-C_{12}.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, aminocyclohexyl, cyclobutyl, aminocyclobutyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl, aminocyclopentyl, and cyclopentyl.

By the term "heterocycloalkyl" as used herein is meant a non-aromatic, unsaturated or saturated, monocyclic or polycyclic, heterocyclic ring containing at least one carbon and at least one heteroatom. Exemplary monocyclic heterocyclic rings include: piperidine, piperazine, pyrrolidine, and morpholine. Exemplary polycyclic heterocyclic rings include quinuclidine.

By the term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one to five substituents, suitably from one to three, selected from the group consisting of: hydrogen, halogen, C1-C6alkyl, amino, trifluoromethyl, $-(CH_2)_nCOOH$, C3-C7cycloalkyl, substituted amino, aryl, heteroaryl, arylalkyl, arylcycloalkyl, heteroarylalkyl, heterocycloalkyl, cyano, hydroxyl, alkoxy, alkylthio, aryloxy, acyloxy, acyl, acylamino, arylamino, nitro, oxo, $-CO_2R_{50}$, $-SO_2R_{70}$, $-NR_{50}SO_2R_{70}$, $NR_{50}C(O)R_{75}$ and $-CONR_{55}R_{60}$, wherein R50 and R55 are each independently selected from: hydrogen, alkyl, and C3-C7cycloalkyl; R55 and R60 can optionally form a heterocycloalkyl ring; n is 0 to 6; R75 is selected from the group consisting of: C1-C6alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, arylamino, C1-C6heterocycloalkyl, substituted C1-C6heterocycloalkyl; each R60 and R70 is independently selected from the group consisting of: C1-C6alkyl, C3-C7cycloalkyl, substituted C1-C6heterocycloalkyl, C1-C6heterocycloalkyl, halogen, amino, substituted amino, arylamino, trifluoromethyl, cyano, hydroxyl, alkoxy, oxo, $-(CH_2)_nCOOH$, aryl optionally fused with a five or six-membered ring or substituted with one to five groups selected from the group consisting of: C1-C6alkyl, C3-C7cycloalkyl, halogen, amino, substituted amino, trifluoromethyl, cyano, hydroxyl, alkoxy, oxo, or $-(CH_2)_nCOOH$, or heteroaryl optionally fused with a five-membered ring or substituted with one to five groups selected from the group consisting of: C1-C6alkyl, C3-C7cycloalkyl, halogen, amino, trifluoromethyl, cyano, hydroxyl, alkoxy, oxo, or $-(CH_2)_nCOOH$.

By the term “substituted”, when referred in the definition of R60, R70, R75, “arylamino”, and “aryloxy”, is meant that the subject chemical moiety has one to five substituents, suitably from one to three, selected from the group consisting of: hydrogen, C1-C6alkyl, halogen, trifluoromethyl, -$(CH_2)_n$COOH, amino, substituted amino, cyano, hydroxyl, alkoxy, alkylthio, aryloxy, acyloxy, acyl, acylamino, and nitro, n is 0-6.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -$OC(O)CH_3$, -$OC(O)CH(CH_3)_2$ and -$OC(O)(CH_2)_3CH_3$.

By the term "acylamino" as used herein is meant -N(H)C(O)alkyl, -N(H)C(O)(cycloalkyl) where alkyl is as described herein. Examples of N-acylamino substituents as used herein include: -$N(H)C(O)CH_3$, -$N(H)C(O)CH(CH_3)_2$ and -$N(H)C(O)(CH_2)_3CH_3$.

By the term “aryloxy” as used herein is meant –O(aryl), -O(substituted aryl), –O(heteroaryl) or –O(substituted heteroaryl).

By the term “arylamino” as used herein is meant -NR_{85}(aryl), -NR_{85}(substituted aryl), -NR_{85}(heteroaryl) or –NR_{85}(substituted heteroaryl), wherein R85 is H, C1-6alkyl or C3-C7cycloalkyl.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein, including alkyl chains defined by the term “-$(CH_2)_n$”, “-$(CH_2)_m$” and the like, is meant a linear or branched, substituted or unsubstituted, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms.

By the term ‘substituted alkyl” as used herein is meant an alkyl group substituted with one to six groups selected from the group consisting of: halogen, trifluoromethyl, alkylcarboxy, amino, substituted amino, cyano, hydroxyl, alkoxy, alkylthio, aryloxy, acyloxy, acyl, acylamino, urea, sulfonamide, carbamate and nitro.

Examples of alkyl and substituted alkyl substituents as used herein include:

$-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH_2-C(CH_3)_3$, $-CH_2-CF_3$, $-C\equiv C-C(CH_3)_3$, $-C\equiv C-CH_2-OH$, cyclopropylmethyl, $-CH_2-C(CH_3)_2-CH_2-NH_2$, $-C\equiv C-C_6H_5$, $-C\equiv C-C(CH_3)_2-OH$, $-CH_2-CH(OH)-CH(OH)-CH(OH)-CH(OH)-CH_2-OH$, piperidinylmethyl, methoxyphenylethyl, $-C(CH_3)_3$, $-(CH_2)_3-CH_3$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH_2-CH_3$, $-CH=CH_2$, and $-C\equiv C-CH_3$.

By the term "treating" and derivatives thereof as used herein, is meant prophylatic and therapeutic therapy. Prophylatic therapy is meant the institution of measures to protect a person from a disease to which he or she has been, or may be, exposed. Also called *preventive treatment*.

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of a PI3 kinase inhibiting compound, as described herein, and a further active ingredient or ingredients. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment. Suitably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

The term “compound” as used herein includes all isomers of the compound. Examples of such isomers include: enantiomers, tautomers, rotamers.

In formulas where a “dotted” bond is drawn between two atoms, it is meant that such bond can be either single or double bond. A ring system containing such bonds can be aromatic or non-aromatic.

Certain compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers, or two or more diastereoisomers. Accordingly, the compounds of this invention include mixtures of enantiomers/diastereoisomers as well as purified enantiomers/diastereoisomers or enantiomerically/diastereoisomerically enriched mixtures. Also included within the

scope of the invention are the individual isomers of the compounds represented by formula I or II above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted. Further, an example of a possible tautomer is an oxo substituent in place of a hydroxy substituent. Also, as stated above, it is understood that all tautomers and mixtures of tautomers are included within the scope of the compounds of Formula I or II.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

It has now been found that compounds of the present invention are inhibitors of the Phosphatoinositides 3-kinases (PI3Ks). When the phosphatoinositides 3-kinase (PI3K) enzyme is inhibited by a compound of the present invention, PI3K is unable to exert its enzymatic, biological or pharmacological effects. The compounds of the present invention are therefore useful in the treatment of autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries.

The compounds of Formula (I) are useful as medicaments in particular for the treatment of autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries. According to one embodiment of the present invention, the compounds of Formula (I) are inhibitors of one or more phosphatoinositides 3-kinases (PI3Ks), suitably, Phosphatoinositides 3-kinase γ

(PI3Kγ), Phosphatoinositides 3-kinase γ (PI3Kα), Phosphatoinositides 3-kinase γ (PI3Kβ), or Phosphatoinositides 3-kinase γ (PI3Kδ).

Compounds according to Formula (I) are suitable for the modulation, notably the inhibition of the activity of phosphatoinositides 3-kinases (PI3K), suitably phosphatoinositides 3-kinase (PI3Kα). Therefore the compounds of the present invention are also useful for the treatment of disorders which are mediated by PI3Ks. Said treatment involves the modulation – notably the inhibition or the down regulation – of the phosphatoinositides 3-kinases.

Suitably, the compounds of the present invention are used for the preparation of a medicament for the treatment of a disorder selected from multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, lung inflammation, thrombosis or brain infection/inflammation, such as meningitis or encephalitis, Alzheimer's disease, Huntington's disease, CNS trauma, stroke or ischemic conditions, cardiovascular diseases such as athero-sclerosis, heart hypertrophy, cardiac myocyte dysfunction, elevated blood pressure or vasoconstriction.

Suitably, the compounds of Formula (I) are useful for the treatment of autoimmune diseases or inflammatory diseases such as multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, lung inflammation, thrombosis or brain infection/inflammation such as meningitis or encephalitis.

Suitably, the compounds of Formula (I) are useful for the treatment of neurodegenerative diseases including multiple sclerosis, Alzheimer's disease, Huntington's disease, CNS trauma, stroke or ischemic conditions.

Suitably, the compounds of Formula (I) are useful for the treatment of cardiovascular diseases such as atherosclerosis, heart hypertrophy, cardiac myocyte dysfunction, elevated blood pressure or vasoconstriction.

Suitably, the compounds of Formula (I) are useful for the treatment of chronic obstructive pulmonary disease, anaphylactic shock fibrosis, psoriasis, allergic diseases, asthma, stroke, ischemic conditions, ischemia-reperfusion, platelets aggregation/activation, skeletal muscle atrophy/hypertrophy, leukocyte recruitment in cancer tissue, angiogenesis, invasion metastasis, in particular melanoma, Karposi's sarcoma, acute and chronic bacterial and virual infections, sepsis, transplantation rejection, graft rejection, glomerulo sclerosis, glomerulo nephritis, progressive renal fibrosis, endothelial and epithelial injuries in the lung, and lung airway inflammation.

Because the pharmaceutically active compounds of the present invention are active as PI3 kinase inhibitors, particularly the compounds that inhibit PI3Kα, either selectively or in conjunction with one or more of PI3Kδ, PI3Kβ, or PI3Kγ, they exhibit therapeutic utility in treating cancer.

Suitably, the invention relates to a method of treating cancer in a mammal, including a human, wherein the cancer is selected from: brain (gliomas), glioblastomas, leukemias, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone and thyroid.

Suitably, the invention relates to a method of treating cancer in a mammal, including a human, wherein the cancer is selected from: Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, Acute megakaryocytic leukemia, promyelocytic leukemia and Erythroleukemia.

Suitably, the invention relates to a method of treating cancer in a mammal, including a human, wherein the cancer is selected from: malignant lymphoma,

hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma and follicular lymphoma.

Suitably, the invention relates to a method of treating cancer in a mammal, including a human, wherein the cancer is selected from: neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

When a compound of Formula (I) is administered for the treatment of cancer, the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of a PI3 kinase inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of cancer in the present invention. Examples of such agents can be found in Cancer Principles and Practice f Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and

anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Examples of a further active ingredient or ingredients for use in combination or co-administered with the present PI3 kinase inhibiting compounds are chemotherapeutic agents.

Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G_2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

Paclitaxel, 5β,20-epoxy-1,2α,4,7β,10β,13α-hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. It was first isolated in 1971 by Wani et al. J. Am. Chem, Soc., 93:2325. 1971), who characterized its structure by chemical and X-ray crystallographic methods. One mechanism for its activity relates to paclitaxel's capacity to bind tubulin, thereby inhibiting cancer cell growth. Schiff et al., Proc. Natl, Acad, Sci. USA, 77:1561-1565 (1980); Schiff et al., Nature, 277:665-667 (1979); Kumar, J. Biol, Chem, 256: 10435-10441 (1981). For a review of synthesis and anticancer activity of some paclitaxel derivatives see: D. G. I. Kingston *et al.*, Studies in Organic Chemistry vol. 26, entitled "New trends in Natural Products Chemistry 1986", Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) pp 219-235.

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman et al., Yale Journal of Biology and Medicine, 64:583, 1991; McGuire et al., Ann. lntem, Med., 111:273,1989) and for the treatment of breast cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797,1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment

of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosupression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer. The primary dose limiting side effects of cisplatin are nephrotoxicity, which may be controlled by hydration and diuresis, and ototoxicity.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma. Bone marrow suppression is the dose limiting toxicity of carboplatin.

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and

chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias. Alopecia, nausea, vomiting and leukopenia are the most common dose limiting side effects of cyclophosphamide.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. Bone marrow suppression is the most common dose limiting side effect of chlorambucil.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia. Bone marrow suppression is the most common dose limiting side effects of busulfan.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. Delayed myelosuppression is the most common dose limiting side effects of carmustine.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is

indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also know as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dactinomycin.

Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma. Myelosuppression is the most common dose limiting side effect of daunorubicin.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination

with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas. Pulmonary and cutaneous toxicities are the most common dose limiting side effects of bleomycin.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G_2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers. Myelosuppression is the most common side effect of etoposide. The incidence of leucopenia tends to be more severe than thrombocytopenia.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide can induce both leucopenia and thrombocytopenia.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Myelosuppression and mucositis are dose limiting side effects of 5-fluorouracil. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1-β-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine). Cytarabine induces leucopenia, thrombocytopenia, and mucositis.

Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression and gastrointestinal mucositis are expected side effects of mercaptopurine at high doses. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of thioguanine administration. However, gastrointestinal side effects occur and can be dose limiting. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

Methotrexate, N-[4[[(2,4-diamino-6-pteridinyl) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair or replication through the inhibition of dyhydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

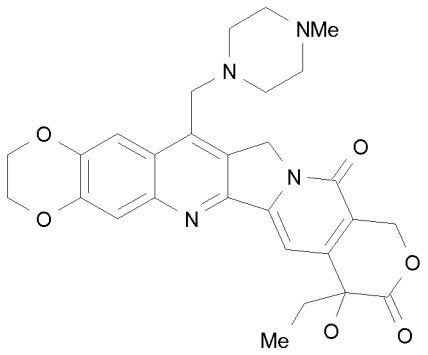
Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irintecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the

colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.

Also of interest, is the camptothecin derivative of formula A following, currently under development, including the racemic mixture (R,S) form as well as the R and S enantiomers:



A

known by the chemical name "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R,S)-camptothecin (racemic mixture) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R)-camptothecin (R enantiomer) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin (S enantiomer). Such compound as well as related compounds are described, including methods of making, in U.S. Patent Nos. 6,063,923; 5,342,947; 5,559,235; 5,491,237 and pending U.S. patent Application No. 08/977,217 filed November 24, 1997.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as

prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children ; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) or follicle stimulating hormone (FSH) for the

treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in

uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor –I (IGFI) receptor, macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, London.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases useful in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta,

gamma, epsilon, mu, lambda, iota, zeta). IkB kinase family (IKKa, IKKb), PKB family kinases, AKT kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), Journal of Biochemistry. 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), Biochemical Pharmacology, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., and Harris, A.L. (1995), Cancer Treatment and Research. 78: 3-27, Lackey, K. et al Bioorganic and Medicinal Chemistry Letters, (10), 2000, 223-226; U.S. Patent No. 6,268,391; and Martinez-Iacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku are also useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), Current Opinion in Immunology. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), Oncogene 17 (25) 3301-3308; Jackson, S.P. (1997), International Journal of Biochemistry and Cell Biology. 29 (7):935-8; and Zhong, H. et al, Cancer res, (2000) 60(6), 1541-1545.

Also useful in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras , thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9 (2) 99 – 102; and BioChim. Biophys. Acta, (19899) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225

EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kniases, Breast cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

Non-receptor kinase angiogenesis inhibitors may also find use in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases). Angiogenesis in general is linked to erbB2/EGFR signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Thus, the combination of an erbB2/EGFR inhibitor with an inhibitor of angiogenesis makes sense. Accordingly, non-receptor tyrosine kinase inhibitors may be used in combination with the EGFR/erbB2 inhibitors of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin ($alpha_v$ $beta_3$) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed erb family inhibitors. (See Bruns CJ et al (2000), Cancer Res., 60: 2926-2935; Schreiber AB, Winkler ME, and Derynck R. (1986), Science, 232: 1250-1253; Yen L et al. (2000), Oncogene 19: 3460-3469).

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). There are a number of immunologic strategies to generate an immune response against erbB2 or EGFR. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of erbB2/EGFR signaling pathways using a small molecule inhibitor. Discussion of the immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT et al. (2000), Cancer Res. 60: 3569-3576; and Chen Y, Hu D, Eling DJ, Robbins J, and Kipps TJ. (1998), Cancer Res. 58: 1965-1971.

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked

to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are discussed in Water JS et al. (2000), J. Clin. Oncol. 18: 1812-1823; and Kitada S et al. (1994), Antisense Res. Dev. 4: 71-79.

Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230.

In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of formula I or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

Because the pharmaceutically active compounds of the present invention are active as PI3 kinase inhibitors, particularly the compounds that modulate/inhibit PI3Kα, either selectively or in conjunction with one or more of PI3Kγ, PI3Kβ, or PI3Kδ, they exhibit therapeutic utility in treating a disease state selected from: autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, cancer, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection and lung injuries.

When a compound of Formula (I) is administered for the treatment of a disease state selected from: autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, cancer, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection or lung injuries, the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of a PI3 kinase inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of autoimmune disorders, inflammatory diseases, cardiovascular diseases, cancer, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection or lung injuries.

Biological assays

Compounds of the present invention were tested according to the following assays and found as inhibitors of PI3 kinases, particularly PI3Kα. The exemplified compounds were tested and found active against PI3Kα. The IC_{50}'s ranged from about 1 nM to 10 μM. The majority of the compounds were under 500 nM; the more active compounds were under 100 nM, the most active compounds were found under 10 nM.

The compound of Example 22 was tested generally according to the assays described herein and in at least one experimental run exhibited a IC50 value: equal to 316 nM against PI3Kα.

The compound of Example 29 was tested generally according to the assays described herein and in at least one experimental run exhibited a IC50 value: equal to 100 nM against PI3Kα.

The compound of Example 27 was tested generally according to the assays described herein and in at least one experimental run exhibited a IC50 value: equal to 631 nM against PI3Kα.

The compound of Example 35 was tested generally according to the assays described herein and in at least one experimental run exhibited a IC50 value: equal to 13 nM against PI3Kα.

PI3K alpha TR-FRET assay

Assay Principle

The PI3-Kinase assay has been developed and optimized from a kit produced by Upstate (Millipore). Briefly, this kit contains a biotinylated PIP3 which forms a HTRF (homogeneous time-resolved fluorescence energy transfer) complex when mixed with a Europium labeled anti-GST monoclonal antibody, a GST tagged pleckstrin homology (PH) domain, and Streptavidin-Allophycocyanin (APC). The unlabeled PIP3 produced by PI 3-Kinase activity displaces biotin-PIP3 from the complex resulting in a loss of energy transfer and thus a decrease in signal.

Millipore, PI 3-Kinase (human) HTRF™ Assay, technical document associated with catalog# 33-017

Assay protocol

Compounds are serially diluted (3-fold in 100% DMSO) across a polypropylene 120 µL mother plate from column 1 to column 12 and column 13 to column 24, leaving columns 6 and 18 containing only DMSO to yield 11 concentrations for each test compound. Once titrations are made, 0.1µL is transferred to the assay plates (Greiner 784075). This assay plate contains three controls: column 6 with DMSO, and column 18 with alternating 20 µM wortmannin and 40 µM PIP3. The wortmannin control is dispensed from a Greiner polypropylene 120 µL mother plate containing > 20µL of 1mM wortmannin into the assay plate via the hummingbird or comparable instrument in wells 18 A, C, E, G, I, K, M, O (0.1µL of 1mM wortmannin in 100% DMSO). The PIP3 control is dispensed into the plate manually via a matrix pipettor, 1µL of 200 µM PIP3 in 1X Reaction buffer to wells 18 B, D, F, H, J, L, N, P.

The PI3-Kinase assay has been developed and optimized from a kit produced by Upstate (Millipore). The assay kit (cat: 33-017) contains seven reagents: 1) 4X Reaction Buffer, 2) PIP2 (1mM), 3) Stop A, 4) Stop B, 5) Detection Mix A, 6) Detection Mix B, 7) Detection Mix C. In addition the following items were obtained or purchased, PI3Kinase (prepared in-house), 4X PI3K Detection Buffer

(Millipore), dithiothreitol (Sigma, D-5545), Adenosine-5'-triphosphate (ATP, Sigma, A-6419), PIP3 (1,2-dioctanoyl-sn-glycero-3-[phosphoinositil-3,4,5-triphosphate] tetraammonium salt (Avanti polar lipids, 850186P), DMSO (Sigma, 472301), Wortmannin (Sigma, W-1628).

Prepare 1X PI3Kinase Reaction Buffer by diluting stock 1:4 with de-ionized water, freshly prepared DTT is added at a final concentration of 5 mM on the day of use. Enzyme addition and compound preincubation is initiated by the addition of 2.5μL of 2X enzyme solution, PI3K alpha in 1X reaction buffer, to all wells using a Multidrop Combi. Plates are incubated at room temperature for 15 minutes. Substrate addition and reaction initiation is completed by the addition of 2.5μL of 2X substrate solution, PIP2 and ATP in 1X reaction buffer, to all wells using a Multidrop Combi. Plates are incubated at room temperature for one hour. Reactions are quenched by the addition of 2.5μL of stop solution (mix Stop A and Stop B in a ratio of 5:1, respectively, i.e.: for a 6000μL total volume, mix 5000μL Stop A and 1000μL Stop B) to all wells using the Multidrop Combi. Followed by the addition of 2.5μL of Detection Reagents Solution (mix Detection mix C, Detection mix A, and Detection mix B together in an 18:1:1 ratio, i.e.: for a 6000 μL total volume, mix 5400 μL Detection mix C, 30 0μL Detection mix A, and 300 μL Detection mix B, note: this solution should be prepared 2 hours prior to use) to all wells using the Mulitdrop Combi, cover plate to avoid exposure to light. Incubate one hour, evaluate the HTRF signal on the Envision plate reader.

Data analysis

The loss of PI3-kinase signal due to product formation leading to biotinylated-PIP3 displacement is nonlinear with respect to both increasing product and time. This non-linear detection will impact accuracy of IC50 calculations; therefore, there is a need for a correction factor or back calculation to obtain a more accurate IC50. The correction varies based on the standard wells of the assay plates (column 6 and 18) of product formed in each assay plate. All data were initially normalized by calculating a ratio of acceptor to donor fluorescence, and %inhibition for each compound concentration was calculated as follows: %inhibition = 100*(signal – CtrlB)/(CtrlA – CtrlB) where CtrlA= PI3Kinase alpha + 10μM Wortmannin and CrtlB= PI3Kinase alpha + DMSO. An IC50 was then calculated fitting the %inhibition data to the equation: %inhibition = min + (max-min)/(1 + ([inhibitor]/IC50)^n) where min is the %inhibition with no inhibitor (typically 0%),

max is the %inhibition with saturating inhibitor (typically 100%), and n is the Hill slope (typically 1). Finally, the IC50 was converted to pIC50 (pIC50 = -log(IC50)), and the pIC50 value was corrected by using plate controls and the equation below: pIC50 (corrected) = pIC50 (observed) + log10((CtrlA-CtrlB)/(CtrlB-CtrlC)), where CtrlA and CtrlB are as defined above and CrtlC= 10μM PI(3,4,5)P3, 100% displacement of biotinylated PI(3,4,5)P3.

PI3K alpha Leadseeker SPA Assay

Assay principle

SPA imaging beads are microspheres containing scintillant which emit light in the red region of the visible spectrum. As a result, these beads are ideally suited to use with a CCD imager such as the Viewlux. The Leadseeker beads used in this system are polystyrene beads that have been coupled with polyethyleneimine. When added to the assay mixture, the beads absorb both the substrate (PIP2) and product (PIP3). Adsorbed P^{33}-PIP3 will cause an increase in signal, measured as ADUs (analog to digital units). This protocol details the use of the PEI-PS Leadseeker beads for assays using His-p110/p85 PI3K alpha.

Assay protocol

Solid compounds are typically plated with 0.1 μl of 100% DMSO in all wells (except column 6 and 18) of a 384-well, flat bottom, low volume plate (Greiner 784075). The compounds are serially diluted (3-fold in 100% DMSO) across the plate from column 1 to column 12 and column 13 to column 24 and leave column 6 and 18 containing only DMSO to yield 11concentraions for each test compound.

The assay buffer contains MOPS (pH 6.5), CHAPS, and DTT. PI3K alpha and PIP2 (L-alpha-D-myo-Phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2]3-O-phospho linked, D(+)-sn-1,2-di-O-octanoylglyceryl, CellSignals # 901) are mixed and incubated in the plate with compound for 30min prior to starting the reaction with the addition of P^{33}-ATP and $MgCl_2$ (reagents added using Zoom). Enzyme-free wells (column 18) are typically done to determine the low control. PEI-PS Leadseeker beads in PBS/EDTA/CHAPS are added (by Multidrop) to quench the reaction, and the plates are allowed to incubate for at least one hour (typically overnight) before centrifugation. The signal is determined using a Viewlux detector and is then imported into curve fitting software (Activity Base) for construction of concentration response curves. The percent inhibition of activity was calculated relative to high controls (C1, 0.1μl DMSO in column 6, rows A-P)) and low controls

(C2, 5 µl of 40 uM PIP2 in buffer in column 18, rows A-P) using, 100*(1-(U1-C2)/(C1-C2)). The concentration of test compound yielding 50% inhibition was determined using the equation, y = ((Vmax*x) / (K+x)) + Y2, where "K" was equal to the IC50. The IC50 values were converted to pIC50 values, i.e., -log IC50 in Molar concentration.

Celluar assays:

DAY 1

- Plate cells before noon
  - 10K cells/well in clear flat-bottomed 96-well plates (*f.v. 105ul*)
  - Last four wells in last column receive media only
  - Place in 37degC incubator overnight
- Compound plate
  - Prepare in polypropylene round-bottomed 96-well plates; 8 compounds per plate, 11-pt titrations of each (3x serial dilution), DMSO in last column (0.15% f.c. on cells)
  - 15ul in first well, 10ul DMSO in the rest; take 5ul from first well and mix in next, continue across plate (*excluding last column*); seal with foil lid and place at 4degC

DAY 2

- Take out Lysis buffer inhibitors (4degC/-20degC) and compound plates (4degC), thaw on bench top; make 1x Tris wash buffer (WB) to fill reservoir on plate washer and top off bench supply (use MiliQ), turn on centrifuge to allow it to cool
- Block MSD plates
  - Make 20ml 3% blocking solution/plate (600mg blocker A in 20ml WB), add 150ul/well and incubate at RT for at least 1 hr
- Add compound (while blocking)
  - Add 300ul growth media (RPMI w/ Q, 10% FBS) per well (682x dil of compound) to each compound plate
  - Add 5ul compound dilution into each well (*f.v. 110ul*) on duplicate plates
  - Place in 37degC incubator for 30min
- Make lysates
  - Prepare MSD Lysis buffer; for 10ml add 200ul protease inhibitor solution, and 100ul each of Phosphatase inhibitors I & II (*Keep on ice until ready for use*)
  - Remove plates post-incubation, aspirate media with plate washer, wash 1x with cold PBS, and add 80ul MSD Lysis buffer per well; incubate on shaker at 4degC for ≥30min
  - Spin cold at 2500rpm for 10min; leave plates in 4degC centrifuge until ready for use

- AKT duplex assay
  - Wash plates (4x with 200ul/well WB in plate washer); tap plates on paper towel to blot
  - Add 60ul of lysates/well, incubate on shaker at RT for 1hr
  - During incubation prepare detection Ab (3ml/plate; 2ml WB and 1ml blocking solution w/ Ab at 10nM); repeat wash step as above
  - Add 25ul of Ab/well, incubate on shaker at RT for 1hr; repeat wash step as above
  - Add 150ul/well 1x Read Buffer (dilute 4x stock in ddH2O, 20ml/plate), read immediately
- Analysis
  - Observe all the data points at each compound concentration.
  - The data point from highest inhibitor concentration must be equal or greater than 70% of DMSO control.
  - IC50 for duplicate runs must be within 2-fold of each other (not flagged in summary template).
  - Y min must be greater than zero; if both mins are red flagged (>35) then compound is listed as inactive (IC50= > highest dose). If only one min is red flagged, but still ≤50 then call IC50 as listed.
  - Any data points equal or greater than 30% off the curve will not be considered.

Cell Growth/Death Assay:

BT474, HCC1954 and T-47D (human breast) were cultured in RPMI-1640 containing 10% fetal bovine serum at 37^0C in 5% CO_2 incubator. Cells were split into T75 flask (Falcon #353136) two to three days prior to assay set up at density which yields approximately 70-80% confluence at time of harvest for assay. Cells were harvested using 0.25% trypsin-EDTA (Sigma #4049). Cell counts were performed on cell suspension using Trypan Blue exclusion staining. Cells were then plated in 384 well black flat bottom polystyrene (Greiner #781086) in 48 µl of culture media per well at 1,000 cells/well. All plates were placed at 5% CO_2, 37^0C overnight and test compounds were added the following day. One plate was treated with CellTiter-Glo (Promega #G7573) for a day 0 (t=0) measurement and read as described below. The test compounds were prepared in clear bottom polypropylene 384 well plates (Greiner#781280) with consecutive two fold dilutions. 4 µl of these dilutions were added to 105 µl culture media, after mixing the solution, 2 µl of these dilutions were added into each well of the cell plates. The final concentration of DMSO in all wells was 0.15%. Cells were incubated at 37^0C, 5% CO_2 for 72 hours.

Following 72 hours of incubation with compounds each plate was developed and read. CellTiter-Glo reagent was added to assay plates using a volume equivalent to the cell culture volume in the wells. Plates were shaken for approximately two minutes and incubated at room temperature for approximately 30 minutes and chemiluminescent signal was read on the Analyst GT (Molecular Devices) reader. Results were expressed as a percent of the t=0 and plotted against the compound concentration. Cell growth inhibition was determined for each compound by fitting the dose response with a 4 or 6 parameter curve fit using XLfit software and determining the concentration that inhibited 50% of the cell growth (gIC50) with the Y min as the t=0 and Y max as the DMSO control. Value from wells with no cells was subtracted from all samples for background correction.

Additional references:

The compounds of the present invention can also be tested to determine their inhibitory activity at PI3Kα, PI3Kδ, PI3Kβ and PI3Kγ according to the following references:

For all PI3K isoforms:

1. Cloning, expression, purification, and characterization of the human Class Ia phosphoinositide 3-kinase isoforms: Meier, T.I.; Cook, J.A.; Thomas, J.E.; Radding, J.A.; Horn, C.; Lingaraj, T.; Smith, M.C. Protein Expr. Purif., 2004, 35(2), 218.
2. Competitive fluorescence polarization assays for the detection of phosphoinositide kinase and phosphatase activity: Drees, B.E.; Weipert, A.; Hudson, H.; Ferguson, C.G.; Chakravarty, L.; Prestwich, G.D. Comb. Chem. High Throughput.Screen., 2003, 6(4), 321.

For PI3Kγ: WO 2005/011686 A1

The pharmaceutically active compounds within the scope of this invention are useful as PI3 Kinase inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating diseases associated with PI3 kinase inhibition, particularly: autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries and other conditions requiring PI3 kinase modulation/inhibition, which comprises administering an effective compound of Formula (I) or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their ability to act as PI3 inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of a PI3K inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include

topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular PI3 kinase inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing PI3 kinase inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective PI3 kinase modulating/inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as a PI3 kinase inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries.

The invention also provides for a pharmaceutical composition for use as a PI3 inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney

diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries, which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

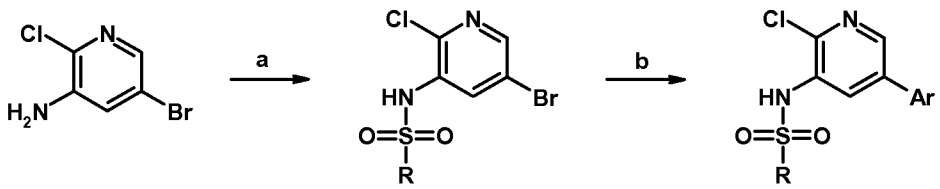
In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, including compounds known to have utility when used in combination with a PI3 kinase inhibitor.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Experimental Details

The derivatives described herein can prepared by the general methods described below. For example, reaction of commercially available 3-amino-5-bromo-2-chloropyrimidine with various sulfonyl chlorides, followed by coupling with aryl (or heteroaryl) boronic acid or aryl (or heteroaryl) boronic ester using standard Suzuki reaction conditions gives the corresponding N-(5-aryl-2-chloro-3-pyridinyl)sulfonamides.

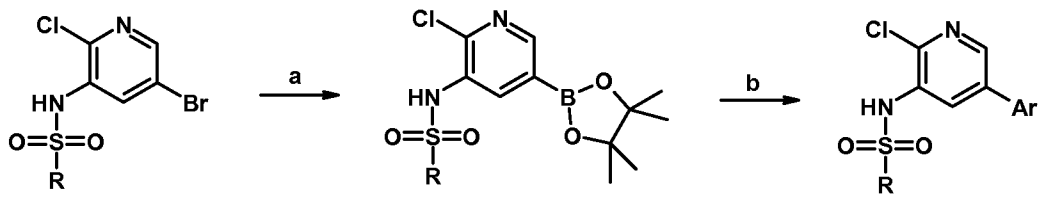
Scheme 1:



Conditions: a) **R**-SO_2Cl, pyridine, methylene chloride, room temperature; b) **Aryl (or heteroaryl)**-boronic acid (or ester), potassium carbonate, palladium catalyst, dioxane, water, heat.

Alternatively, conversion of the N-(5-bromo-2-chloro-3-pyridinyl)sulfonamides to the corresponding boronates, followed by coupling with aryl (or heteroaryl)-halides using standard Suzuki reaction conditions gives the corresponding N-(5-aryl-2-chloro-3-pyridinyl)sulfonamides.

Scheme 2:

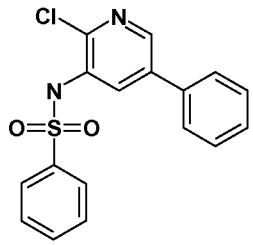


Conditions: a) bis(pinacolato)diboron, potassium acetate, palladium catalyst, N,N-dimethylformamide, heat; b) **Aryl (or heteroaryl)**-halide, potassium carbonate, palladium catalyst, dioxane, water, heat.

Experimentals

Example 1

N-(2-chloro-5-phenyl-3-pyridinyl)benzenesulfonamide



a) *N*-(5-bromo-2-chloro-3-pyridinyl)benzenesulfonamide

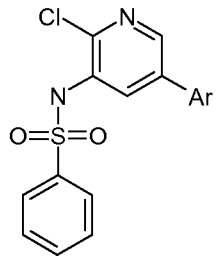
To a stirred solution of 3-amino-5-bromo-2-chloropyridine (5.0 g, 24 mMol) in CH_2Cl_2 (50 mL) was added pyridine (5.0 mL, 61.8 mMol) followed by benzenesulfonyl chloride (6 mL, 47 mMol) drop wise over 5 minutes. The reaction was stirred at RT for 3 days and evaporated to dryness under vacuum. (LCMS showed only 1% starting material remained, 55% desired product and 44% di-sulfonylated product.) The residue which remained was taken up in MeOH (50 mL) and treated with K_2CO_3 (10 g, 72.3 mMol) and H_2O (1 mL). The suspension was stirred and refluxed (80 °C oil bath) for 1 h. (LCMS showed complete conversion of

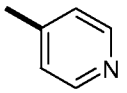
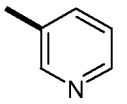
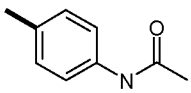
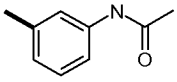
the di-sulfonylated product to the title compound.) The reaction was evaporated to near dryness and poured into a solution of NH_4Cl (25 g) in H_2O (200 mL). The suspension was stirred for 30 minutes (resultant pH ~7-8), filtered through a fine sintered glass funnel, washed with cold H_2O, and dried under vacuum. Purified by flash chromatography on silica gel (5 to 10% MeOH/CH_2Cl_2). The slightly colored solid was triturated with (1:1) CH_2Cl_2/hexanes, filtered and dried under vacuum to give the title compound (7.77 g, 93%) as a off-white solid: LCMS >97% pure, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.61 (br. s., 1 H), 8.41 (d, *J* = 2.27 Hz, 1 H), 7.91 (d, *J* = 2.27 Hz, 1 H), 7.73 - 7.77 (m, 2 H), 7.67 - 7.72 (m, 1 H), 7.56 - 7.64 (m, 2 H); MS (ES) m/e 346.8 $(M + H)^+$.

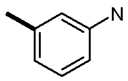
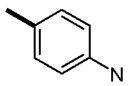
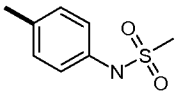
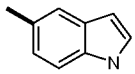
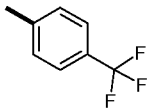
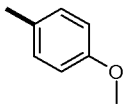
b) *N*-(2-chloro-5-phenyl-3-pyridinyl)benzenesulfonamide

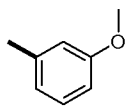
To a 25 mL seal tube was added *N*-(5-bromo-2-chloro-3-pyridinyl) benzenesulfonamide (200 mg, 0.57 mmol), phenylboronic acid (63 mg, 0.52 mmol), and potassium carbonate (216 mg, 1.57 mmol) in 1,4-dioxane (8 ml) and water (4 ml). The reaction mixture was degassed by nitrogen, and tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.028 mmol) was added. The tube was sealed and the reaction mixture was heated to 105 °C for 18 hr . Water (1 mL) followed by ethyl acetate (15 mL) and acetic acid (0.5 mL) were added. Organic layer was separated, washed with sat NaCl, dried over $MgSO_4$, filtered and evaporated. Solid was recrystalized from acetonitrile:water. *N*-(2-chloro-5-phenyl-3-pyridinyl)benzenesulfonamide was isolated as a white powder (50 mg, 28 % yield). 1H NMR (400 MHz, MeOD) δ ppm 7.43 - 7.50 (m, 1 H) 7.50 - 7.58 (m, 4 H) 7.60 - 7.66 (m, 3 H) 7.77 - 7.86 (m, 2 H) 8.16 (d, *J*=2.27 Hz, 1 H) 8.43 (d, *J*=2.27 Hz, 1 H) LC-MS (m/e) = 345.0 (MH+). Rt = 1.63 min

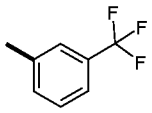
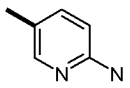
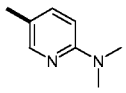
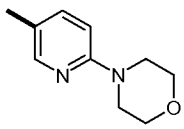
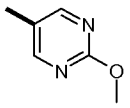
Following examples were prepared from commercial available aryl or heteroaryl boronic acids or esters coupled with N-(5-bromo-2-chloro-3-pyridinyl)benzenesulfonamide following procedure described in Example 1. Products were isolated by crystallization or by purification by preparative HPLC using water (0.1% formic acid) : acetonitrile (0.1% formic acid) as a mobile phase.

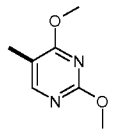


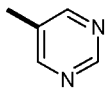
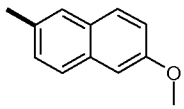
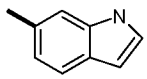
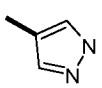
Example	Ar	NMR	LC-MS (m/e)
2		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.58 (t, *J*=7.58 Hz, 2 H) 7.63 - 7.82 (m, 5 H) 7.96 (s, 1 H) 8.07 (d, *J*=2.27 Hz, 1 H) 8.57 - 8.82 (m, 3 H) 10.53 (br. s., 1 H)	346.0
3		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.50 - 7.63 (m, 3 H) 7.63 - 7.72 (m, 1 H) 7.72 - 7.80 (m, 2 H) 7.97 - 8.03 (m, 1 H) 8.05 - 8.12 (m, 1 H) 8.53 - 8.72 (m, 2 H) 8.87 (d, *J*=1.77 Hz, 1 H) 10.49 (br. s., 1 H)	346.0
4		1H NMR (400 MHz, DMSO-d_6) δ ppm 2.08 (s, 3 H) 7.54 - 7.64 (m, 4 H) 7.65 - 7.72 (m, 2 H) 7.75 (dd, *J*=9.09, 7.58 Hz, 3 H) 7.87 (d, *J*=2.27 Hz, 1 H) 8.53 (d, *J*=2.27 Hz, 1 H) 10.13 (s, 1 H) 10.41 (s, 1 H)	402.0
5		1H NMR (400 MHz, DMSO-d_6) δ ppm 2.09 (s, 3 H) 7.31 (d, *J*=8.08 Hz, 1 H) 7.44 (t, *J*=7.83 Hz, 1 H) 7.54 - 7.62 (m, 2 H) 7.62 - 7.71 (m, 2 H) 7.74 - 7.84 (m, 2 H) 7.89 (d, *J*=2.27 Hz, 2 H) 8.47 (d, *J*=2.27 Hz, 1 H) 10.13 (s, 1 H) 10.48 (br. s., 1 H)	402.0

6		1H NMR (400 MHz, MeOD) δ ppm 6.76 - 6.84 (m, 1 H) 6.86 - 6.93 (m, 1 H) 6.95 (t, *J*=1.89 Hz, 1 H) 7.24 (t, *J*=7.83 Hz, 1 H) 7.50 - 7.58 (m, 2 H) 7.61 - 7.69 (m, 1 H) 7.77 - 7.86 (m, 2 H) 8.12 (d, *J*=2.27 Hz, 1 H) 8.35 (d, *J*=2.27 Hz, 1 H)	360.0
7		1H NMR (400 MHz, MeOD) δ ppm 6.82 (m, 2 H) 7.37 (m, 2 H) 7.49 - 7.58 (m, 2 H) 7.60 - 7.68 (m, 1 H) 7.76 - 7.85 (m, 2 H) 8.05 (d, *J*=2.27 Hz, 1 H) 8.33 (d, *J*=2.27 Hz, 1 H)	360.0
8		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.06 (s, 3 H) 7.33 (m, *J*=8.59 Hz, 2 H) 7.52 - 7.65 (m, 4 H) 7.67 (d, *J*=7.58 Hz, 1 H) 7.76 (m, *J*=8.59 Hz, 2 H) 7.88 (d, *J*=2.27 Hz, 1 H) 8.51 (d, *J*=2.02 Hz, 1 H) 10.00 (s, 1 H) 10.42 (s, 1 H)	438.0
9		1H NMR (400 MHz, MeOD) δ ppm 6.57 (d, *J*=2.27 Hz, 1 H) 7.33 (d, *J*=3.03 Hz, 1 H) 7.35 (dd, *J*=8.59, 1.77 Hz, 1 H) 7.49 - 7.59 (m, 3 H) 7.61 - 7.69 (m, 1 H) 7.78 - 7.89 (m, 3 H) 8.17 (d, *J*=2.53 Hz, 1 H) 8.43 (d, *J*=2.53 Hz, 1 H)	384.0
10		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.59 (t, *J*=7.58 Hz, 2 H) 7.65 - 7.73 (m, 1 H) 7.73 - 7.80 (m, 2 H) 7.89 (s, 4 H) 8.02 (d, *J*=2.53 Hz, 1 H) 8.64 (d, *J*=2.27 Hz, 1 H) 10.51 (s, 1 H)	413.0
11		1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.89 (s, 3 H) 7.00 - 7.07 (m, 3 H) 7.46 - 7.55 (m, 4 H) 7.58 - 7.64 (m, 1 H) 7.79 - 7.88 (m, 2 H) 8.18 (d, *J*=2.27 Hz, 1 H) 8.32 (d, *J*=2.27 Hz, 1 H)	375.0

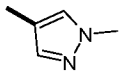
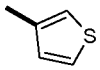
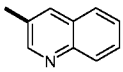
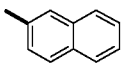
12		1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.90 (s, 3 H) 7.01 (dd, *J*=7.83, 2.02 Hz, 1 H) 7.03 - 7.09 (m, 2 H) 7.12 - 7.16 (m, 1 H) 7.44 (t, *J*=7.96 Hz, 1 H) 7.51 (t, *J*=7.71 Hz, 2 H) 7.57 - 7.68 (m, 1 H) 7.78 - 7.91 (m, 2 H) 8.21 (d, *J*=2.02 Hz, 1 H) 8.35 (d, *J*=2.27 Hz, 1 H)	375.0

13		1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.11 (s, 1 H) 7.50 - 7.56 (m, 2 H) 7.61 - 7.70 (m, 2 H) 7.71 - 7.78 (m, 3 H) 7.82 - 7.89 (m, 2 H) 8.19 (d, *J*=2.27 Hz, 1 H) 8.36 (d, *J*=2.27 Hz, 1 H)	413.0
14		1H NMR (400 MHz, DMSO-d_6) δ ppm 6.34 (s, 2 H) 6.55 (d, *J*=8.59 Hz, 1 H) 7.53 - 7.63 (m, 2 H) 7.63 - 7.72 (m, 2 H) 7.72 - 7.81 (m, 3 H) 8.14 (s, 1 H) 8.17 (d, *J*=2.53 Hz, 1 H) 8.45 (d, *J*=2.27 Hz, 1 H)	361.0
15		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.08 (s, 6 H) 6.75 (d, *J*=8.59 Hz, 1 H) 7.58 (t, *J*=7.45 Hz, 2 H) 7.62 - 7.72 (m, 1 H) 7.72 - 7.84 (m, 4 H) 8.14 (s, 2 H) 8.36 (d, *J*=2.27 Hz, 1 H) 8.45 (d, *J*=2.02 Hz, 1 H)	389.2
16		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.46 - 3.61 (m, 4 H) 3.64 - 3.81 (m, 4 H) 6.96 (d, *J*=8.84 Hz, 1 H) 7.59 (t, *J*=7.58 Hz, 2 H) 7.64 - 7.73 (m, 1 H) 7.73 - 7.80 (m, 2 H) 7.85 (td, *J*=4.48, 2.65 Hz, 2 H) 8.42 (d, *J*=2.27 Hz, 1 H) 8.54 (d, *J*=2.27 Hz, 1 H) 10.39 (br. s., 1 H)	431.2
17		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.99 (s, 3 H) 7.58 (t, *J*=7.71 Hz, 2 H) 7.62 - 7.72 (m, 1 H) 7.73 - 7.79 (m, 2 H) 8.05 (d, *J*=2.53 Hz, 1 H) 8.60 (d, *J*=2.27 Hz, 1 H) 8.93 (s, 2 H) 10.47 (br. s., 1 H)	377.0

18		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.92 (s, 3 H) 3.96 (s, 3 H) 7.61 (t, *J*=7.45 Hz, 2 H) 7.65 - 7.74 (m, 1 H) 7.75 - 7.84 (m, 2 H) 7.89 (d, *J*=2.27 Hz, 1 H) 8.39 (d, *J*=2.27 Hz, 1 H) 8.47 (s, 1 H) 10.45 (br. s., 1 H)	407.0

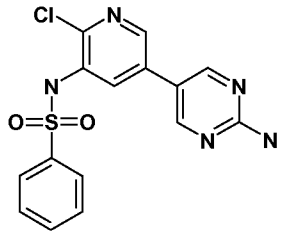
19		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.58 (t, *J*=7.71 Hz, 2 H) 7.63 - 7.72 (m, 1 H) 7.76 (d, *J*=7.33 Hz, 2 H) 8.14 (d, *J*=1.77 Hz, 1 H) 8.67 (d, *J*=1.77 Hz, 1 H) 9.14 (s, 2 H) 9.27 (s, 1 H) 10.52 (br. s., 1 H)	347.0
20		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.91 (s, 3 H) 7.25 (dd, *J*=9.09, 2.53 Hz, 1 H) 7.40 (d, *J*=2.27 Hz, 1 H) 7.61 (t, *J*=7.71 Hz, 2 H) 7.70 (d, *J*=7.33 Hz, 1 H) 7.74 (dd, *J*=8.59, 1.77 Hz, 1 H) 7.76 - 7.83 (m, 2 H) 7.90 - 7.99 (m, 2 H) 8.02 (d, *J*=2.27 Hz, 1 H) 8.15 (d, *J*=1.52 Hz, 1 H) 8.68 (d, *J*=2.27 Hz, 1 H) 10.45 (s, 1 H)	425.0
21		1H NMR (400 MHz, DMSO-d_6) δ ppm 6.49 (d, *J*=2.27 Hz, 1 H) 7.24 (dd, *J*=8.34, 1.52 Hz, 1 H) 7.43 - 7.50 (m, 1 H) 7.57 - 7.75 (m, 5 H) 7.75 - 7.85 (m, 2 H) 7.88 (d, *J*=2.27 Hz, 1 H) 8.56 (d, *J*=2.27 Hz, 1 H) 10.41 (s, 1 H) 11.32 (br. s., 1 H)	384.0
22		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.58 (t, *J*=7.58 Hz, 2 H) 7.64 - 7.71 (m, 1 H) 7.71 - 7.78 (m, 2 H) 7.88 (d, *J*=2.27 Hz, 1 H) 8.34 (br. s., 1 H) 8.53 (d, *J*=2.02 Hz, 1 H) 10.30 (s, 1 H) 13.18 (br. s., 1 H)	355.0

23		1H NMR (400 MHz, DMSO-d_6) δ ppm 6.98 (d, *J*=1.01 Hz, 1 H) 7.58 (t, *J*=7.58 Hz, 2 H) 7.66 (d, *J*=7.33 Hz, 1 H) 7.71 - 7.79 (m, 2 H) 7.82 (t, *J*=1.64 Hz, 1 H) 7.90 (d, *J*=2.27 Hz, 1 H) 8.33 (s, 1 H) 8.51 (d, *J*=1.77 Hz, 1 H) 10.37 (br. s., 1 H)	335.0

24		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.88 (s, 3 H) 7.58 (t, *J*=7.58 Hz, 2 H) 7.64 - 7.71 (m, 1 H) 7.72 - 7.78 (m, 2 H) 7.85 (d, *J*=2.27 Hz, 1 H) 7.91 (s, 1 H) 8.28 (s, 1 H) 8.48 (d, *J*=2.27 Hz, 1 H) 10.33 (s, 1 H)	349.0
25		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 - 7.63 (m, 3 H) 7.63 - 7.71 (m, 1 H) 7.71 - 7.78 (m, 3 H) 7.99 (d, *J*=2.27 Hz, 1 H) 8.06 (dd, *J*=2.91, 1.39 Hz, 1 H) 8.64 (d, *J*=2.27 Hz, 1 H) 10.40 (s, 1 H)	351.0
26		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.60 (t, *J*=7.58 Hz, 3 H) 7.64 - 7.76 (m, 2 H) 7.76 - 7.81 (m, 2 H) 7.81 - 7.92 (m, 1 H) 8.10 (d, *J*=8.34 Hz, 2 H) 8.14 (d, *J*=2.27 Hz, 1 H) 8.69 (d, *J*=2.02 Hz, 1 H) 8.75 (br. s., 1 H) 9.17 (d, *J*=2.27 Hz, 1 H) 10.52 (br. s., 1 H)	396.0
27		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.54 - 7.65 (m, 4 H) 7.68 - 7.75 (m, 1 H) 7.79 (dd, *J*=8.34, 1.26 Hz, 3 H) 7.94 - 8.12 (m, 4 H) 8.23 (d, *J*=1.52 Hz, 1 H) 8.72 (d, *J*=2.27 Hz, 1 H) 10.48 (s, 1 H)	395.0

Example 28

N-[5-(2-amino-5-pyrimidinyl)-2-chloro-3-pyridinyl]benzenesulfonamide



a) *N*-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide

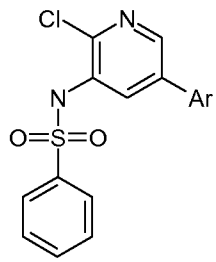
To a 100 mL round-bottomed flask was added N-(5-bromo-2-chloro-3-pyridinyl) benzenesulfonamide (4.1 g, 11.79 mmol), pinacoladodiborane (3.59 g, 14.15 mmol), and potassium acetate (3.47 g, 35.4 mmol) in N,N-dimethylformamide (DMF) (50 ml).The reaction mixture was degassed by nitrogen, and $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.482 g, 0.590 mmol) was added. The reaction mixture was heated to 90 °C overnight. N,N-Dimethylformamide was evaporated, black oil dissolved in DCM, 2 g of decolorizing carbon was added. The reaction mixture was stirred for 10 min, and then filtered through short pad of silica. Black oil was evaporated, and the residue was purified via Analogix (hexane:ethyl acetate 30 to 70 %). Only colorless fraction with product has been collected (not the yellow one) and evaporated. Solid was suspended in hexane and filtered. Pure N-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (2.39 g, 5.45 mmol, 46.2 % yield) was isolated and dried under vacuum overnight. 1H NMR (400 MHz, CHLOROFORM-*d*) d ppm 1.37 (s, 12 H) 6.94 (s, 1 H) 7.48 (t, *J*=7.71 Hz, 2 H) 7.59 (d, *J*=7.58 Hz, 1 H) 7.79 (dd, *J*=8.59, 1.26 Hz, 2 H) 8.35 (d, *J*=1.77 Hz, 1 H) 8.44 (d, *J*=1.52 Hz, 1 H).

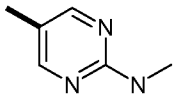
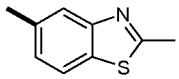
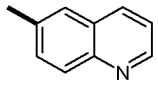
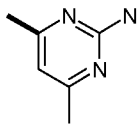
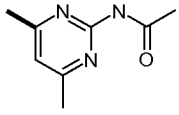
b) *N*-[5-(2-amino-5-pyrimidinyl)-2-chloro-3-pyridinyl]benzenesulfonamide

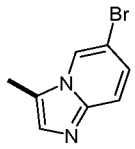
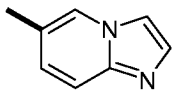
To a 25 mL seal tube (t=g) was added N-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (131 mg, 0.33 mmol), 2-amino-5-bromopyrimidine (57 mg, 0.33 mmol), and potassium carbonate (138 mg, 1

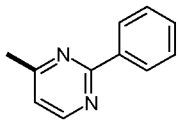
mmol) in 1,4-dioxane (8 ml) and water (4 ml). The reaction mixture was degassed by nitrogen, and tetrakis(triphenylphosphine)palladium(0) (14.64 mg, 0.013 mmol) was added. The tube was sealed and the reaction mixture was heated to 105 °C for 18 hr . Water (1 mL) followed by ethyl acetate (15 mL) and acetic acid (0.5 mL) were added. Organic layer was separated, washed with sat NaCl, dried over MgSO4, filtered and evaporated. Product purified by prep. HPLC (0.1% formic acid, 5 to 95% water:acetonitrile). Fractions were combined and evaporated. N-[5-(2-amino-5-pyrimidinyl)-2-chloro-3-pyridinyl]benzenesulfonamide (48 mg, 40 % yield) was isolated as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 7.01 (s, 2 H) 7.58 (t, *J*=7.58 Hz, 2 H) 7.62 - 7.72 (m, 1 H) 7.72 - 7.80 (m, 2 H) 7.85 (d, *J*=2.27 Hz, 1 H) 8.49 (d, *J*=2.27 Hz, 1 H) 8.53 (s, 2 H) 10.38 (br. s., 1 H) LC-MS (m/e) = 362.0 (MH+). Rt = 1.19 min

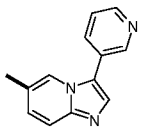
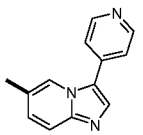
The following examples were prepared from aryl or heteroaryl bromides or chlorides coupled with pure N-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide following procedure described in Example 28b. Products were isolated by crystallization or by purification by preparative HPLC using water (0.1% formic acid) : acetonitrile (0.1% formic acid) as a mobile phase.

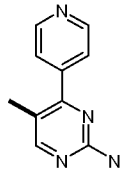
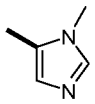


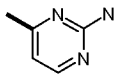
Example	Ar	NMR	LC-MS (m/e)
29		1H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (d, *J*=4.80 Hz, 3 H) 7.47 (q, *J*=4.63 Hz, 1 H) 7.57 (t, *J*=7.58 Hz, 2 H) 7.61 - 7.71 (m, 1 H) 7.71 - 7.80 (m, 2 H) 7.84 (d, *J*=2.27 Hz, 1 H) 8.46 (d, *J*=1.52 Hz, 1 H) 8.56 (br. s., 2 H) 10.38 (br. s., 1 H)	376.0
30		1H NMR (400 MHz, MeOD) δ ppm 2.88 (s, 3 H) 7.50 - 7.62 (m, 2 H) 7.62 - 7.75 (m, 2 H) 7.77 - 7.90 (m, 2 H) 8.02 - 8.13 (m, 2 H) 8.22 (d, *J*=2.27 Hz, 1 H) 8.50 (d, *J*=2.27 Hz, 1 H)	416.0
31		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.55 - 7.65 (m, 3 H) 7.65 - 7.73 (m, 1 H) 7.76 - 7.82 (m, 2 H) 8.05 (dd, *J*=8.72, 2.15 Hz, 1 H) 8.10 (d, *J*=2.27 Hz, 1 H) 8.13 - 8.19 (m, 1 H) 8.32 (d, *J*=1.77 Hz, 1 H) 8.47 (dd, *J*=8.46, 1.14 Hz, 1 H) 8.72 (d, *J*=2.02 Hz, 1 H) 8.97 (dd, *J*=4.29, 1.77 Hz, 1 H) 10.50 (br. s., 1 H)	396.0
32		1H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 - 2.40 (m, 3 H) 6.75 (s, 2 H) 7.09 (s, 1 H) 7.59 (t, *J*=7.58 Hz, 2 H) 7.62 - 7.72 (m, 1 H) 7.72 - 7.81 (m, 2 H) 8.39 (d, *J*=2.27 Hz, 1 H) 8.84 (d, *J*=2.27 Hz, 1 H) 10.47 (br. s., 1 H)	376.0
33		1H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.49 (s, 3 H) 7.56 (t, *J*=7.58 Hz, 2 H) 7.61 - 7.69 (m, 1 H) 7.71 (s, 1 H) 7.76 - 7.85 (m, 2 H) 8.50 (d, *J*=2.02 Hz, 1 H) 8.90 (br. s., 1 H) 10.51 (br. s., 1 H) 10.57 (s, 1 H)	418.0

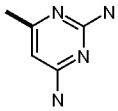
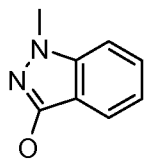
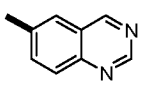
34		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.49 (dd, *J*=9.60, 1.77 Hz, 1 H) 7.58 (t, *J*=7.58 Hz, 2 H) 7.63 - 7.73 (m, 2 H) 7.75 - 7.82 (m, 2 H) 7.89 (s, 1 H) 8.00 (d, *J*=2.27 Hz, 1 H) 8.49 (d, *J*=1.52 Hz, 1 H) 8.66 (d, *J*=1.01 Hz, 1 H) 10.58 (br. s., 1 H)	465.0
35		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.53 (dd, *J*=9.35, 1.77 Hz, 1 H) 7.58 (t, *J*=7.58 Hz, 2 H) 7.63 - 7.81 (m, 5 H) 7.97 - 8.09 (m, 2 H) 8.57 (d, *J*=2.27 Hz, 1 H) 9.02 (s, 1 H) 10.60 (br. s., 1 H)	385.2

36		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.57 - 7.67 (m, 5 H) 7.67 - 7.77 (m, 1 H) 7.79 - 7.96 (m, 2 H) 8.11 (d, *J*=5.31 Hz, 1 H) 8.30 - 8.48 (m, 2 H) 8.52 (d, *J*=2.27 Hz, 1 H) 9.03 (d, *J*=5.31 Hz, 1 H) 9.09 (d, *J*=2.02 Hz, 1 H) 10.63 (br. s., 1 H)	423.0

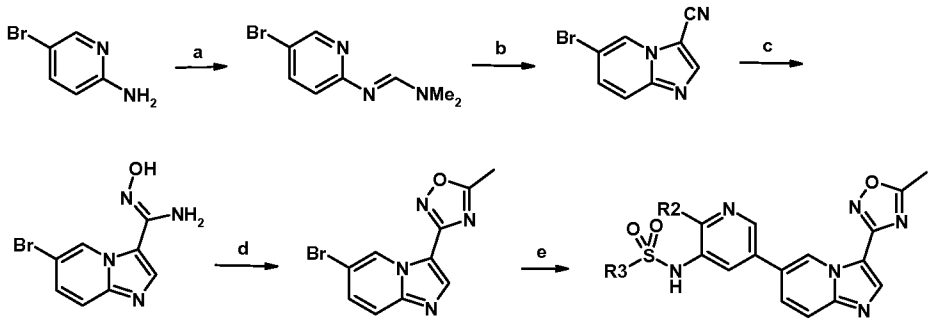
37		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.49 - 7.69 (m, 5 H) 7.69 - 7.78 (m, 2 H) 7.85 (d, *J*=9.35 Hz, 1 H) 7.96 (s, 1 H) 8.01 (d, *J*=2.53 Hz, 1 H) 8.25 (dt, *J*=8.27, 1.80 Hz, 1 H) 8.65 (d, *J*=2.27 Hz, 1 H) 8.68 (dd, *J*=4.80, 1.77 Hz, 1 H) 8.77 (s, 1 H) 8.98 (d, *J*=1.52 Hz, 1 H) 10.49 (br. s., 1 H)	462.0
38		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.56 (t, *J*=7.58 Hz, 2 H) 7.60 - 7.68 (m, 2 H) 7.73 - 7.78 (m, 2 H) 7.82 - 7.90 (m, 3 H) 8.05 (d, *J*=2.27 Hz, 1 H) 8.08 - 8.18 (m, 1 H) 8.66 (d, *J*=2.02 Hz, 1 H) 8.69 - 8.77 (m, 2 H) 8.92 (s, 1 H) 10.51 (br. s., 1 H)	462.0

39		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.10 (br. s., 2 H) 7.18 (d, *J*=5.81 Hz, 2 H) 7.34 (d, *J*=2.02 Hz, 1 H) 7.48 (t, *J*=7.33 Hz, 2 H) 7.52 - 7.68 (m, 4 H) 8.14 (s, 1 H) 8.21 (br. s., 1 H) 8.52 (d, *J*=5.81 Hz, 2 H)	439.0
40		1H NMR (400 MHz, DMSO-d_6) δ ppm 3.54 - 3.72 (m, 3 H) 7.18 (s, 1 H) 7.58 (t, *J*=7.45 Hz, 2 H) 7.61 - 7.70 (m, 1 H) 7.72 (d, *J*=2.27 Hz, 1 H) 7.74 - 7.80 (m, 2 H) 7.84 (s, 1 H) 8.14 (s, 1 H) 8.31 (d, *J*=1.52 Hz, 1 H) 10.66 (br. s., 1 H)	349.0

41		1H NMR (400 MHz, DMSO-d_6) δ ppm 6.86 (s, 2 H) 7.17 (d, *J*=5.05 Hz, 1 H) 7.53 - 7.63 (m, 2 H) 7.63 - 7.72 (m, 1 H) 7.73 - 7.81 (m, 2 H) 8.38 (d, *J*=5.05 Hz, 1 H) 8.41 (d, *J*=2.02 Hz, 1 H) 8.85 (s, 1 H) 10.48 (s, 1 H)	362.0

42		1H NMR (400 MHz, DMSO-d_6) δ ppm 6.19 (s, 3 H) 6.65 (br. s., 2 H) 7.51 - 7.61 (m, 2 H) 7.61 - 7.70 (m, 1 H) 7.72 - 7.82 (m, 2 H) 8.14 (s, 2 H) 8.18 (s, 1 H) 8.57 (br. s., 1 H)	377.0
43		1H NMR (400 MHz, DMSO-*d*6) δ ppm 3.84 (br. s., 3 H) 7.20 (s, 1 H) 7.59 (t, *J*=7.45 Hz, 2 H) 7.64 - 7.81 (m, 5 H) 7.97 (br. s., 1 H) 8.59 (br. s., 1 H)	461.0
44		^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.55 (s, 1H), 9.71 (s, 1H), 9.37 (s, 1H), 8.77 (d, *J*=4.0 Hz, 1 H), 8.53 (d, *J*=4.0 Hz, 1 H), 8.36 (dd, *J*=8.0, 4.0 Hz, 1 H), 8.18-8.16 (m, 2H), 7.79-7.77 (m, 2H), 7.70 (m, 1H), 7.63-7.59 (m, 2H). LC-MS (m/e) = 398.0 (MH+, very broadened)	398.0

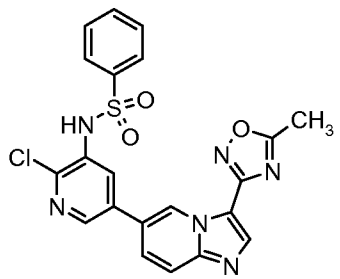
Scheme 3:



Conditions: a) *N*,*N*-dimethyl-1,1-bis(methyloxy)methanamine, MeOH, heat; b) bromoacetonitrile, sodium bicarbonate, isopropanol, heat; c) hydroxylamine hydrochloride, triethylamine, ethanol; d) acetic anhydride, toluene, heat; e) optionally substituted pyridylboronate, tetrakis(triphenylphosphine)palladium(0), sodium bicarbonate, dioxane, water, heat.

Example 45

N-{2-chloro-5-[3-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-*a*]pyridin-6-yl]-3-pyridinyl}benzenesulfonamide



a) *N*'-(5-bromo-2-pyridinyl)-*N*,*N*-dimethylimidoformamide

To a solution of 2-amino-5-bromopyridine (5.0 g, 28.9 mmol), in dry MeOH was added DMF-DMA (12.7 mL, 95.4 mmol) in a sealable reaction tube. The reaction was purged with nitrogen, sealed and heated to 70 °C. After 5.5 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting solid was recrystallized from hexanes to give 4.1 g (62%) of *N*'-(5-bromo-2-pyridinyl)-*N*,*N*-dimethylimidoformamide as a yellow solid. MS(ES)+ m/e 228 $[M+H]^+$.

b) 6-bromoimidazo[1,2-*a*]pyridine-3-carbonitrile

To a mixture of *N'*-(5-bromo-2-pyridinyl)-*N*,*N*-dimethylimidoformamide (3.8 g, 16.7 mmol) in i-PrOH (80 mL) was added bromoacetonitrile (2.3 mL, 33.4 mmol) followed by $NaHCO_3$ (3.5 g, 41.8 mmol) in a sealable reaction tube. The reaction was purged with nitrogen, sealed and heated to 100 °C. After 1 h, the reaction mixture was concentrated under reduced pressure and the residue was suspended in water (100 mL). The precipitate was collected by filtration and triturated with boiling acetonitrile to give 1.39 g (37%) of 6-bromoimidazo[1,2-*a*]pyridine-3-carbonitrile as a brown solid. MS(ES)+ m/e 222.8 $[M+H]^+$.

c) 6-bromo-*N*-hydroxyimidazo[1,2-*a*]pyridine-3-carboximidamide

To a suspension of 6-bromoimidazo[1,2-*a*]pyridine-3-carbonitrile (2.0 g, 9.0 mmol) in EtOH (90 mL), was added hydroxylamine-hydrochloride (0.62 g, 9.0 mmol) and triethylamine (2.5 mL, 18.0 mmol) to gradually give a clear brown solution. After 1 h, an additional portion of hydroxylamine-hydrochloride (0.030 g, 0.45 mmol) was added. After a total of 3 h, the reaction mixture was concentrated under reduced pressure and the residue was triturated with water and stirred vigorously. The precipitate was collected by filtration and dried to constant weight to provide 2.05 (89%) of 6-bromo-*N*-hydroxyimidazo[1,2-*a*]pyridine-3-carboximidamide as a dark tan solid. MS(ES)+ m/e 239.7, 241.7 $[M+H]^+$.

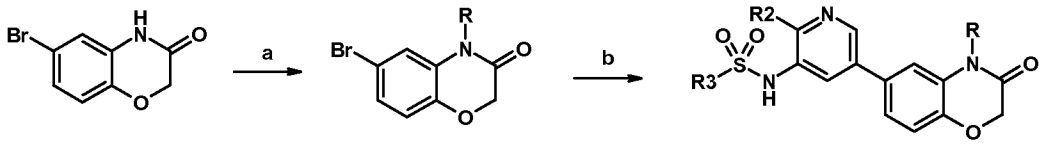
d) 6-bromo-3-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-*a*]pyridine

To a sealable reaction tube was added 6-bromo-*N*-hydroxyimidazo[1,2-*a*]pyridine-3-carboximidamide (1.95 g, 7.65 mmol), toluene (75 mL) and acetic anydride (7.2 mL, 76.5 mmol). The reaction tube was sealed and heated to 100 °C for 6 h. The reaction mixture was allowed to cool to rt and concentrated under reduced pressure. The solid residue was triturated with warm acetonitrile and the precipitate was collected by filtration to give 1.80 g (80%) of 6-bromo-3-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-*a*]pyridine as a brown solid. MS(ES)+ m/e 278.8, 280.9 $[M+H]^+$.

e) *N*-{2-chloro-5-[3-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-*a*]pyridin-6-yl]-3-pyridinyl}benzenesulfonamide:

To a sealable reaction tube was added N-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (150 mg, 0.38 mmol), 6-bromo-3-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-*a*]pyridine (106 mg, 0.38 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.015 mmol), 1,4-dioxane (2 ml) and a suspension of sodium bicarbonate (128 mg, 1.52 mmol) in water (0.75 ml). The reaction mixture was purged with nitrogen, sealed and heated to 100 °C for 17 h. The reaction mixture was allowed to cool to room temperature, 1 mL of sat aqueous NaCl was added and the top dioxane layer was loaded directly onto a silica gel column and purified (Analogix, 80 g column, EtOAc). The clean fractions (TLC) were combined and concentrated under reduced pressure. The resultant solid was suspended in EtOAc (5 mL) and heated gently (to dissolve any triphenylphosphine oxide), allowed to cool and the precipitate was collected by filtration and dried to constant weight under high vacuum to give 35 mg (20%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.28 (bs, 1H), 8.64 (s, 1 H), 8.40 (s, 1H), 8.05 (d, *J*=4.0 Hz, 1 H), 7.99 (d, *J*=8.0 Hz, 1 H), 7.87-7.82 (m, 3H), 7.70 (m, 1H), 7.63-7.59 (m, 2H), 2.75 (s, 3H). LC-MS (m/e) = 467.0 (MH+).

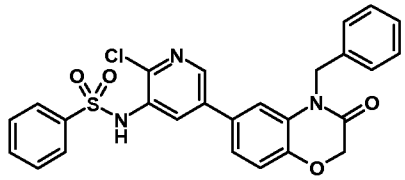
Scheme 4:



Conditions: a) **R**-Br, potassium carbonate, benzyltriethylammonium chloride, acetonitrile, heat; b) bis(pinacolato)diboron, dichloro 1,1'-bis(diphosphino)ferrocene palladium, potassium acetate, dioxane, heat; then optionally susbstituted pyridylsulfonamide, dichloro 1,1'-bis(diphosphino)ferrocene palladium. 2 M aqueous potassium carbonate, heat.

Example 46

N-{2-chloro-5-[3-oxo-4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]-3-pyridinyl}benzenesulfonamide



a) 6-bromo-4-(phenylmethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one

A mixture of 6-bromo-2*H*-1,4-benzoxazin-3(4*H*)-one (0.300 g, 1.316 mmol), benzyl bromide (0.450 g, 2.632 mmol), solid potassium carbonate (0.455 g, 3.29 mmol), and benzyltriethylammonium chloride (0.150 g, 0.658 mmol) in dry acetonitrile (60 mL) was refluxed overnight. The cooled reaction was diluted with EtOAc (100mL), washed with 1 N HCl (3 x 30 mL) and saturated NaCl, dried over sodium sulfate, filtered and concentrated to yield a white semi-solid. This semi-solid was triturated with hexanes and the resulting solid was filtered and dried in a Buchner funnel to give the title compound (0.350 g, 84%) as a white solid. MS(ES)$^+$ m/e 318 [M+H].

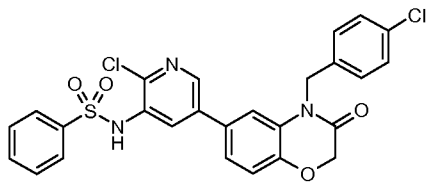
b) *N*-{2-chloro-5-[3-oxo-4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]-3-pyridinyl}benzenesulfonamide

A mixture of 6-bromo-4-(phenylmethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one (0.169 g, 0.532 mmol), bis(pinacolato)diboron (0.135 g, 0,532 mmol), dichloro 1,1'-bis(diphosphino)ferrocene palladium (II) (0.013 g, 0.016 mmol), and solid potassium acetate (0.209 g, 2.128 mmol) in 1,4-dioxane (5 mL) was refluxed for 2 h. The reaction was cooled briefly and to the mixture was added *N*-(5-bromo-2-chloro-3-pyridinyl)benzenesulfonamide (0.185 g, 0.532 mmol), dichloro 1,1'-bis(diphosphino)ferrocene palladium (II) (0.022 g, 0.027 mmol), and 2M aqueous K_2CO_3 (0.294 g, 2.128 mmol, 1.064 mL). The reaction was refluxed for 2h and concentrated in vacuo. The residue was triturated with 50 mL of 10%MeOH:EtOAc, filtered, and the concentrated filtrate was purified by flash chromatography on silica gel (1% MeOH:CH_2Cl_2) to give a white foam.

Recrystallization from MeCN gave the title compound (0.076 g, 28%) as a white solid. MS(ES)$^+$ m/e 506 [M+H].

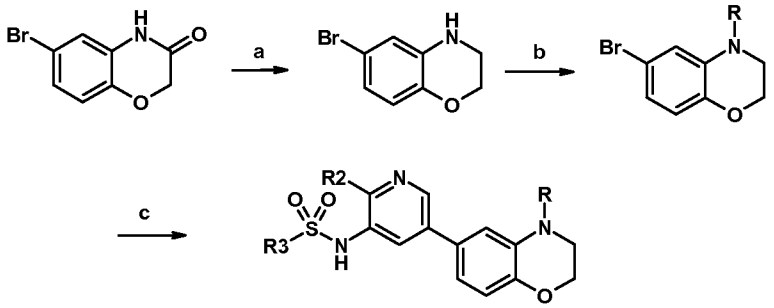
Example 47

N-(2-chloro-5-{4-[(4-chlorophenyl)methyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl}-3-pyridinyl)benzenesulfonamide



Substituting 4-chlorobenzyl bromide for benzyl bromide and triturating with boiling EtOH instead of recrystallizing from MeCN, the title compound was prepared as a white solid (34%). MS(ES)$^+$ m/e 540 [M+H].

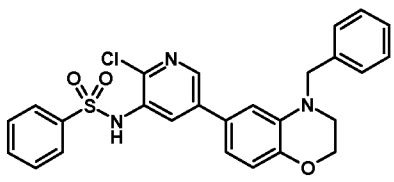
Scheme 5:



Conditions: a) 1 M borane-tetrahydrofuran complex, tetrahydrofuran; b) **R**-Br, potassium carbonate, dimethylformamide, ambient temperature; c) bis(pinacolato)diboron, dichloro 1,1'-bis(diphosphino)ferrocene palladium, potassium acetate, dioxane, heat; then optionally susbstituted pyridylsulfonamide, dichloro 1,1'-bis(diphosphino)ferrocene palladium. 2 M aqueous potassium carbonate, heat.

Example 48

N-{2-chloro-5-[4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]-3-pyridinyl}benzenesulfonamide



a) 6-bromo-3,4-dihydro-2*H*-1,4-benzoxazine

6-Bromo-2*H*-1,4-benzoxazin-3(4*H*)-one (2.085 g, 9.143 mmol) was suspended in dry THF (20 mL) and placed under nitrogen with stirring and to this was added 1 M BH_3-THF complex (3.143 g, 36.572 mmol, 36.52 mL) over 5 minutes. Addition causes the reaction to become homogeneous. After 70 minutes, the reaction was cooled to 0°C and made acidic by addition of 3N HCl (109 mL). Addition of acid causes vigorous bubbling. After the addition was completed, the reaction was refluxed for 10 minutes and then cooled and made basic by addition of 6N NaOH. The basified reaction was extracted with EtOAc (3 x 100 mL), dried over Na_2SO_4, filtered, and the concentrated filtrate was purified by flash chromatography on silica gel (!00% CH_2Cl_2) to give the title compound (1.713 g, 88%) as a pale yellow oil. $MS(ES)^+$ m/e 214 [M+H].

b) 6-bromo-4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazine

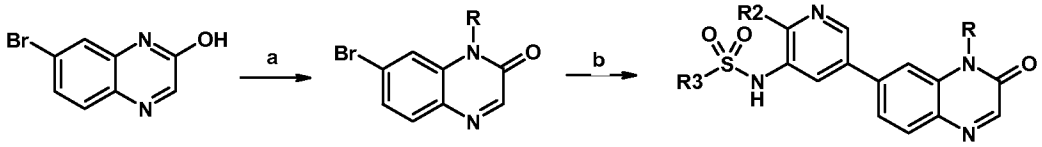
A suspension of 6-bromo-3,4-dihydro-2*H*-1,4-benzoxazine (0.150 g, 0.70 mmol), potassium carbonate (0.242 g, 1.75 mmol), and benzyl bromide (0.179 g, 1.049 mmol) in dry DMF (1.5 mL) was stirred overnight at room temperature. The reaction was diluted with water and EtOAc and transferred to a separatory funnel. The layers were separated and the water was extracted twice with EtOAc. The combined EtOAc layers were washed with water and saturated NaCl, dried over Na_2SO_4, filtered and concentrated to give the title compound (0.203 g, 95%) as a slightly pink crystalline solid. $MS(ES)^+$ m/e 305 [M+H].

c) *N*-{2-chloro-5-[4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]-3-pyridinyl}benzenesulfonamide

A mixture of 6-bromo-4-(phenylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazine (0.199 g, 0.654 mmol), bis(pinacolato)diboron (0.166 g, 0,654 mmol), dichloro 1,1'-bis(diphosphino)ferrocene palladium (II) (0.016 g, 0.02 mmol), and solid potassium acetate (0.257 g, 2.62 mmol) in 1,4-dioxane (5 mL) was refluxed for 80 minutes. The reaction was cooled briefly and to the mixture was added *N*-(5-bromo-2-chloro-3-pyridinyl)benzenesulfonamide (0.227 g, 0.654 mmol), dichloro 1,1'-bis(diphosphino)ferrocene palladium (II) (0.027 g, 0.033 mmol), and 2M aqueous K_2CO_3 (0.362 g, 2.62 mmol, 1.2 mL). The reaction was refluxed for 1 h and concentrated in vacuo. The residue was triturated with 50 mL of

10%MeOH:EtOAc, filtered, and the concentrated filtrate was purified by flash chromatography on silica gel (1% MeOH:CH_2Cl_2) to give a white solid. Recrystallization from MeCN gave the title compound (0.085 g, 26%) as a white solid. MS(ES)$^+$ m/e 492 [M+H].

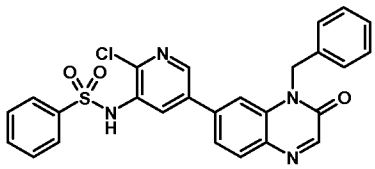
Scheme 6:



Conditions: a) Sodium hydride, dimethylformamide; then **R**-Br, ambient temperature; b) bis(pinacolato)diboron, dichloro 1,1'-bis(diphosphino)ferrocene palladium, potassium acetate, dioxane, heat; then optionally susbstituted pyridylsulfonamide, dichloro 1,1'-bis(diphosphino)ferrocene palladium. 2 M aqueous potassium carbonate, heat.

Example 49

N-{2-chloro-5-[3-oxo-4-(phenylmethyl)-3,4-dihydro-6-quinoxalinyl]-3-pyridinyl}benzenesulfonamide



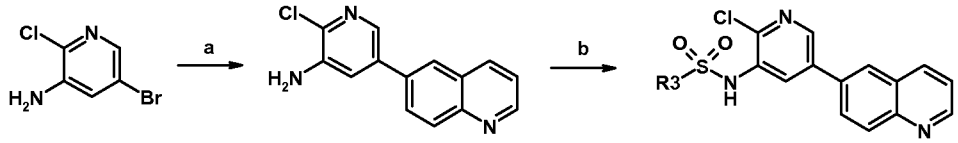
a) 7-bromo-1-(phenylmethyl)-2(1*H*)-quinoxalinone

A slurry of sodium hydride (0.056 g, 2.33 mmol, 0.094 g of 60%) in dry DMF (1.0 mL) was stirred for 5 minutes at room temperature under N_2 and then cooled to 0°C. A solution of 7-bromo-2(1*H*)-quinoxalinone (0.350 g, 1.555 mmol) in DMF (2.5 mL) was added and stirred for 20 minutes at 0°C and to this was added a solution of benzyl bromide (0.292 g, 1.71 mmol) in DMF (1.0 mL). The reaction was stirred overnight at room temperature, diluted with water and EtOAc, and the separated EtOAc layer was washed with water and saturated NaCl, dried over Na_2SO_4, filtered, and the concentrated filtrate was purified by flash chromatography on silica gel (1% MeOH:CH_2Cl_2) to give the title compound (0.237 g, 48%) as a pale yellow solid. MS(ES)$^+$ m/e 315.7 [M+H].

b) *N*-{2-chloro-5-[3-oxo-4-(phenylmethyl)-3,4-dihydro-6-quinoxalinyl]-3-pyridinyl}benzenesulfonamide

A mixture of 7-bromo-1-(phenylmethyl)-2(1*H*)-quinoxalinone (0.077 g, 0.244 mmol), bis(pinacolato)diboron (0.062 g, 0,244 mmol), dichloro 1,1'-bis(diphosphino)ferrocene palladium (II) (0.006 g, 0.007 mmol), and solid potassium acetate (0.096 g, 0.977 mmol) in 1,4-dioxane (4 mL) was refluxed for 60 minutes. The reaction was cooled briefly and to the mixture was added *N*-(5-bromo-2-chloro-3-pyridinyl)benzenesulfonamide (0.085 g, 0.244 mmol), dichloro 1,1'-bis(diphosphino)ferrocene palladium (II) (0.010 g, 0.012 mmol), and 2 M aqueous K_2CO_3 (0.135 g, 0.977 mmol, 0.49 mL). The reaction was refluxed for 1.5 h and concentrated in vacuo. The residue was suspended in 3% MeOH:CH_2Cl_2, filtered through glass wool, and the concentrated filtrate was purified by flash chromatography on silica gel (3% MeOH:CH_2Cl_2) to give a tan solid. Recrystallization from MeCN gave the title compound (0.018 g, 15%) as a tan solid. MS(ES)$^+$ m/e 502.8 [M+H].

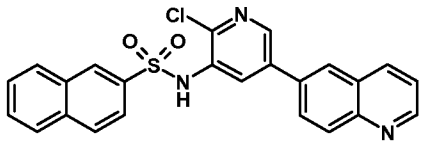
Scheme 7:



Conditions: a) 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline, palladium tetrakis(triphenylphosphine), potassium carbonate, dioxane, water, heat; b) **R3**-SO_2Cl, pyridine, ambient temperature.

Example 50

N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-2-naphthalenesulfonamide



a) 2-chloro-5-(6-quinolinyl)-3-pyridinamine

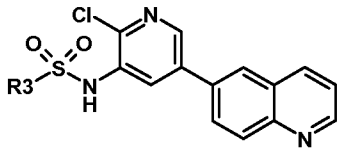
To a 50 mL round-bottomed flask was added 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (0.5 g, 1.960 mmol), 5-bromo-2-chloro-3-pyridinamine (0.407 g, 1.960 mmol), and potassium carbonate (0.813 g, 5.88 mmol) in 1,4-

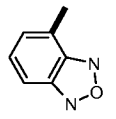
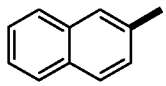
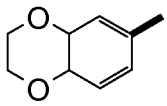
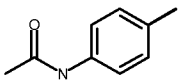
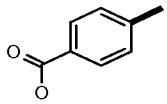
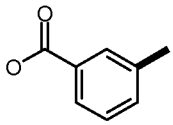
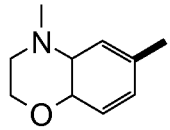
dioxane (10 ml) and water (5 ml) The reaction mixture was degassed by nitrogen, and palladium tetrakis(triphenylphosphine) (0.113 g, 0.098 mmol) was added. The reaction mixture was heated at reflux for 5 hr. Water (1 mL), followed by ethyl acetate (15 mL) were added. Organic layer was separated, washed with sat NaCl, dried over MgSO4, filtered and evaporated. Solid was dissolved in dichloromethane and filtered. 95 % pure 2-chloro-5-(6-quinolinyl)-3-pyridinamine (280 mg, 1.040 mmol, 53.1 % yield) was isolated and used for the next step. 1H NMR (400 MHz, DMSO-d_6) δ ppm 5.75 (s, 2 H) 7.53 (d, *J*=2.02 Hz, 1 H) 7.59 (dd, *J*=8.34, 4.04 Hz, 1 H) 8.01 (dd, *J*=8.72, 2.15 Hz, 1 H) 8.05 (d, *J*=2.27 Hz, 1 H) 8.09 - 8.16 (m, 1 H) 8.26 (d, *J*=2.02 Hz, 1 H) 8.43 - 8.51 (m, 1 H) 8.93 (dd, *J*=4.29, 1.77 Hz, 1 H). LC-MS (m/e) = 256.0 (MH+). Rt = 1.20 min.

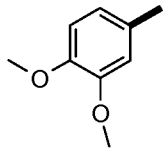
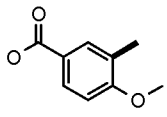
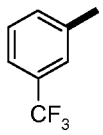
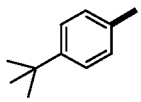
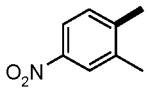
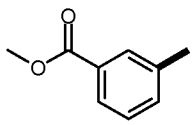
b) *N*-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-2-naphthalenesulfonamide

In a 10 mL sealed tube was added 2-chloro-5-(6-quinolinyl)-3-pyridinamine (50 mg, 0.196 mmol) in 1.5 mL solvent pyridine to give a yellow solution, which was treated with 4-biphenylsulfonyl chloride (59.3 mg, 0.24 mmol) in pyridine (1 mL). The reaction mixture was sealed and stirred at room temperature overnight. The reaction mixture was followed by LCMS. When reaction was done the pyridine was evaporated to dryness. The crude oil was dissolved in acetonitrile/water and purified by preparative HPLC using water (0.1 % TFA): acetonitrile (01. % TFA) as a mobile phase. N-[2-chloro-5-(6-quinolinyl)-3-pyridinyl]-4-biphenylsulfonamide was isolated as a yellow solid (60 mg, 61.8% yield). 1H NMR (400 MHz, DMSO-*d6*) δ ppm 7.39 - 7.56 (m, 3 H) 7.63 (dd, *J*=8.21, 4.17 Hz, 1 H) 7.75 (d, *J*=7.33Hz, 2 H) 7.86 (m, 2 H) 7.93 (m, 2 H) 8.02 - 8.21 (m, 3 H) 8.35 (d, *J*=1.77 Hz, 1 H) 8.46 (d, *J*=7.33 Hz, 1 H) 8.77 (d, *J*=2.27 Hz, 1 H) 8.99 (dd, *J*=4.17, 1.64 Hz, 1 H) 10.56 (br. s., 1 H).

The following examples were prepared from 2-chloro-5-(6-quinolinyl)-3-pyridinamine and commercial available aryl sulfonyl chloride following the procedure described in Example 50.

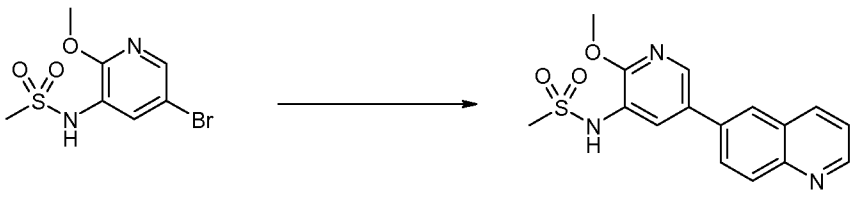


Example	R3	NMR	LC-MS (m/e)
51		1H NMR (400 MHz, DMSO-d_6) δ ppm 7.69 (dd, J=8.21, 4.17 Hz, 1 H) 7.74 (dd, J=9.09, 6.82 Hz, 1 H) 8.07 (d, J=6.32 Hz, 1 H) 8.17 – 8.21 (m, 2 H) 8.37 (d, J=2.53 Hz, 1 H) 8.48 (s, 1 H) 8.56 (d, J=8.34Hz, 1 H) 8.83 (d, J=2.53, 1 H.) 9.02 (dd, J=4.29, 1.52 Hz, 1 H)	438
52		1H NMR (400 MHz, DMSO-d6) δ ppm 7.58 - 7.70 (m, 1 H) 7.66 (dd, J=15.92, 7.83 Hz, 1 H) 7.74 (t, J=6.95Hz, 1 H) 7.86 (dd, J=8.72, 1.89 Hz, 1 H) 8.00 (dd, J=8.84, 2.02 Hz, 1 H) 8.05 - 8.13 (m, 3 H) 8.18 (dd, J=8.21, 3.41 Hz, 2 H) 8.26 (d, J=1.52 Hz, 1 H) 8.40 (d, J=8.82Hz, 1 H) 8.47 (d, J=1.52 Hz, 1 H) 8.73 (d, J=2.53 Hz, 1 H) 8.97 (dd, J=4.17, 1.64 Hz, 1 H) 10.6 (s, 1H)	446
53		1H NMR (400 MHz, DMSO-*d*6) δ ppm 4.28 – 4.33 (m, 4 H) 7.06 (d,*J*=8.08 Hz, 1 H) 7.19 - 7.35 (m, 2 H) 7.67 (dd, *J*=8.21, 4.17 Hz, 1 H) 8.01 - 8.14 (m, 2 H) 8.14 - 8.24 (m, 1 H)8.37 (d, *J*=2.02 Hz, 1 H) 8.52 (s, 1 H) 8.74 (d, *J*=2.27 Hz, 1 H) 9.00 (dd, *J*=4.29, 1.77 Hz, 1 H) 10.35 (s, 1 H)	454
54		1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.08 (s, 3 H) 7.59 - 7.83 (m, 4 H) 8.03 - 8.22 (m, 3 H) 8.36 (d, *J*=1.77 Hz, 1 H) 8.55 (s, 1 H) 8.74 (d, *J*=2.27 Hz, 1 H) 9.02 (dd, *J*=4.42, 1.64 Hz, 1 H) 10.36 (d, *J*=13.89 Hz, 2 H)	453
55		1H NMR (400 MHz, DMSO-*d*6) δ ppm 7.64 (dd, *J*=8.21, 4.17 Hz, 1 H) 7.88 (d, *J*=8.59 Hz, 2 H) 8.03 - 8.24(m, 4 H) 8.37 (d, *J*=1.77 Hz, 1 H) 8.50 (d, *J*=7.33 Hz, 1 H) 8.79 (d, *J*=2.53 Hz, 1 H) 8.98 (dd, *J*=4.17, 1.64 Hz, 1H)	440
56		1H NMR (400 MHz, DMSO-*d*6) δ ppm 7.64 (dd, *J*=8.34, 4.29 Hz, 1 H) 7.75 (t, *J*=7.83 Hz, 1 H) 7.99 (dd,*J*=9.47, 1.64 Hz, 1 H) 8.05 - 8.12 (m, 1 H) 8.13 - 8.19 (m, 2 H) 8.20 - 8.28 (m, 1 H) 8.33 (t, *J*=1.77 Hz, 1 H)8.36 (d, *J*=2.02 Hz, 1 H) 8.49 (d, *J*=7.33 Hz, 1 H) 8.78 (d, *J*=2.27 Hz, 1 H) 8.98 (dd, *J*=4.17, 1.64 Hz, 1 H) 10.70 (s, 1H) 13.55 (s, 1H)	440
57		1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.78 (s, 3 H) 3.26 – 3.28 (m, 2H) 4.28 (d, *J*=4.55 Hz, 2 H) 6.83 (d, *J*=8.59 Hz, 1 H) 6.97 - 7.08 (m, 2 H) 7.66 (dd, *J*=8.21, 4.17 Hz, 1 H) 7.98-8.09 (m, 1 H) 8.04 (d, *J*=2.27 Hz, 1 H) 8.12 - 8.21 (m, 1 H) 8.32 (d, *J*=2.02 Hz, 1 H) 8.50 (s, 1 H) 8.72 (d,*J*=2.27 Hz, 1 H) 8.99 (dd, *J*=4.29, 1.52 Hz, 1 H) 10.19 (s, 1 H)	467

58		1H NMR (400 MHz, DMSO-*d*6) δ ppm 3.75 (s, 3 H) 3.83 (s, 3 H) 7.12 (d, *J*=8.34 Hz, 1 H) 7.25 - 7.36 (m, 1H) 7.71 (dd, *J*=8.34, 4.55 Hz, 1 H) 8.07 - 8.12 (m, 1 H) 8.15 - 8.24 (m, 1 H) 8.37 (d, *J*=2.02 Hz, 1 H) 8.58 (d, *J*=7.83 Hz, 1 H) 8.74 (d, *J*=2.27 Hz, 1 H) 9.03 (dd, *J*=4.42, 1.64 Hz, 1 H) 10.31 (s, 1 H)	456
59		1H NMR (400 MHz, DMSO-*d*6) δ ppm 3.82 (s, 3 H) 7.35 (d, *J*=8.84 Hz, 1 H) 7.68 (dd, *J*=8.34,4.29 Hz, 1 H) 8.05 - 8.25 (m, 4 H) 8.39 (d, *J*=2.02 Hz, 1 H) 8.54 (d, *J*=7.33 Hz, 1 H) 8.74 (d, *J*=2.27 Hz, 1 H) 9.02 (s, 1H) 10.39 (s, 1H) 13.15 (br,s 1H)	470
60		1H NMR (400 MHz, DMSO-*d*6) δ ppm 7.67 (dd, *J*=7.96, 4.17 Hz, 1 H) 7.86 (t, *J*=7.83 Hz, 1 H) 8.00 - 8.25(m, 6 H) 8.42 (s, 1 H) 8.53 (d, *J*=8.08 Hz, 1 H) 8.80 (d, *J*=2.53 Hz, 1 H) 9.00 (d, *J*=2.53 Hz, 1 H)	464
61		1H NMR (400 MHz, DMSO-*d*6) δ ppm 1.28 (s, 9 H) 7.57 - 7.77 (m, 5 H) 8.06 (d, *J*=2.53 Hz, 2 H) 8.17 (d,*J*=8.84 Hz, 1 H) 8.40 (d, *J*=2.02 Hz, 1 H) 8.58 (d, *J*=8.08 Hz, 1 H) 8.75 (d, *J*=2.53 Hz, 1 H) 9.02 (dd, *J*=4.42,1.64 Hz, 1 H) 10.42 (s, 1 H)	452
62		1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.77 (s, 3 H) 7.69 (dd, *J*=8.34, 4.29 Hz, 1 H) 7.79 (d, *J*=8.08 Hz, 1 H)8.07 - 8.23 (m, 2 H) 8.26 (d, *J*=2.53 Hz, 1 H) 8.37 - 8.47 (m, 3 H) 8.54 (d, *J*=1.26 Hz, 1 H) 8.80 (d, *J*=2.53 Hz, 1 H) 9.02 (dd, *J*=4.29, 1.77 Hz, 1 H)	455
63		1H NMR (400 MHz, MeOD) δ ppm 3.93 (s, 3 H) 7.70 (t, *J*=7.83 Hz, 1 H) 7.96 - 8.11 (m, 2 H) 8.28 (dd,*J*=7.83, 1.26 Hz, 1 H) 8.32 - 8.49 (m, 4 H) 8.59 (d, *J*=1.77 Hz, 1 H) 8.69 (d, *J*=2.27 Hz, 1 H) 9.10 (d, *J*=8.34 Hz, 1 H) 9.19 (dd, *J*=5.18, 1.64 Hz, 1 H)	454

Example 64

N-[2-(Methyloxy)-5-(6-quinolinyl)-3-pyridinyl]methanesulfonamide

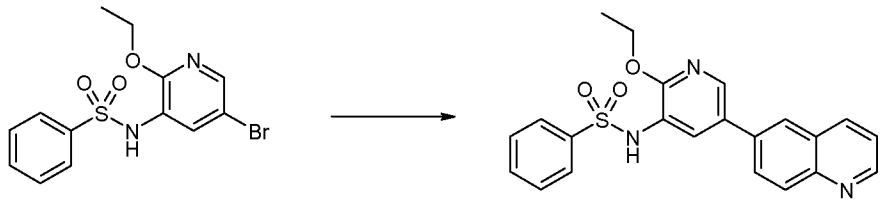


A mixture of *N*-[5-bromo-2-(methyloxy)-3-pyridinyl]methanesulfonamide (0.200 g, 0.711 mmol), 6-quinolinylboronic acid (0.123 g, 0.711 mmol),

dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.029 g, 0.036 mmol), and 2 M aqueous potassium carbonate (0.393 g, 2.85 mmol) in 1,4-dioxane (7 mL) was heated at reflux for 3 hours and concentrated in vacuo. The residue was purified by chromatography on silica gel (100% EtOAc) to give the title compound (0.081 g, 35%) as a white solid. MS(ES)$^+$ m/e 330.1 [M+H].

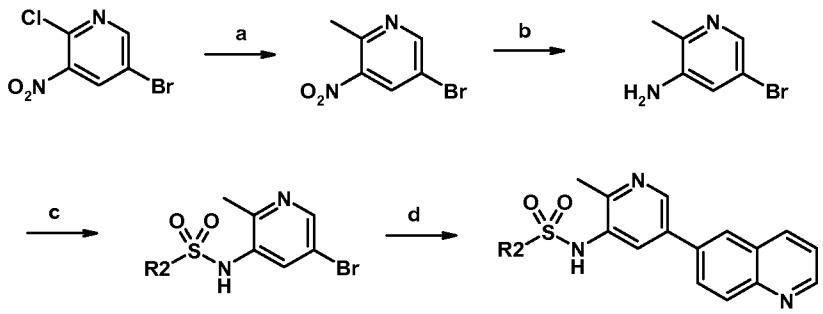
Example 65

N-[2-(Ethyloxy)-5-(6-quinolinyl)-3-pyridinyl]benzenesulfonamide



A slurry of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (257 mg, 1.008 mmol), N-[5-bromo-2-(ethyloxy)-3-pyridinyl]benzenesulfonamide (300 mg, 0.840 mmol) , $PdCl_2(dppf)$-CH_2Cl_2 (34.3 mg, 0.042 mmol) and 2 M aqueous sodium carbonate (1.680 mL, 3.36 mmol) in 1,4-dioxane (6.80 mL) was heated at 95 °C for 20 h. The reaction was cooled to room temperature then treated with silica powder (~3 grams) and decolorizing charcoal (~500 mg), then diluted with methanol and evaporated under reduced pressure to give a dark powder. This was placed on a short pad of silica and rinsed with 10% methanol in ethyl acetate. The filtrate was concentrated to a residue then dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate (2x) and brine, then dried over anhydrous sodium sulfate. The organics were filtered, concentrated to a residue then purified by silica chromatography (40% hexanes in ethyl acetate). The desired fractions were combined and concentrated to give the title compound (227 mg, 66%) as a white solid. MS(ES)+ m/e 406.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-*d*6) δ ppm 1.10 (t, *J*=7.07 Hz, 4 H) 4.11 (q, *J*=7.07 Hz, 3 H) 7.52 - 7.61 (m, 1 H) 7.57 (d, *J*=7.83 Hz, 3 H) 7.63 (d, *J*=7.33 Hz, 1 H) 7.77 (d, *J*=7.07 Hz, 2 H) 7.76 (s, 1 H) 8.01 - 8.06 (m, 2 H) 8.07 - 8.15 (m, 1 H) 8.22 (d, *J*=1.77 Hz, 1 H) 8.42 (d, *J*=2.53 Hz, 1 H) 8.44 (d, *J*=8.59 Hz, 1 H) 8.91 (dd, *J*=4.17, 1.64 Hz, 1 H) 9.98 (s, 1 H).

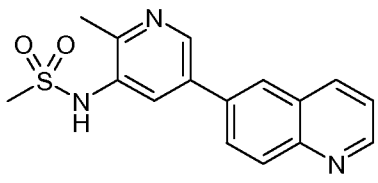
Scheme 8:



Conditions: a) sodium hydride, diethyl malonate, THF; then 6 N HCl, reflux; b) tin(II)chloride dihydrate, ethyl acetate, reflux; c) **R2**-SO_2Cl, pyridine (or **R2**-SO_2Cl, triethylamine, methylene chloride); d) 6-quinolinylboronic acid, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, 2 M aqueous potassium carbonate, dioxane, heat.

Example 66

N-[2-Methyl-5-(6-quinolinyl)-3-pyridinyl]methanesulfonamide



a) 5-bromo-2-methyl-3-nitropyridine

Sodium hydride (1.31 g, 54.8 mmol; 2.19 g of 60% in mineral oil) was suspended in dry THF (70 mL) and to this suspension was added 5-bromo-2-chloro-3-nitropyridine as a solid. An ambient water bath was placed under the reaction and a solution of diethyl malonate in dry THF (15 mL) was added carefully via addition funnel. A vigorous evolution of gas was observed. After 2 hours additional sodium hydride (0.202 g, 8.42 mmol, 0.337 g of 60% in mineral oil) was added and the reaction was stirred for 1.5 hours. The reaction was concentrated in vacuo, diluted with 6 N HCl (100 mL), and heated at reflux overnight. The reaction was concentrated in vacuo and diluted with saturated sodium carbonate until the pH = 9. The basic aqueous mixture was diluted with dichloromethane and filtered through filter paper to remove an insoluble green solid. The filtrate was transferred to a separatory funnel and the layers were separated. The dichloromethane was washed

with brine, dried over Na_2SO_4, filtered and concentrated to give the title compound (5.79 g, 63.3%) as an orange oil. $MS(ES)^+$ m/e 217 [M+H].

b) 5-bromo-2-methyl-3-pyridinamine

A mixture of 5-bromo-2-methyl-3-nitropyridine (5.68 g, 26.2 mmol) and tin (II) chloride dihydrate in EtOAc (200 mL) was heated at reflux for 2 hours and concentrated in vacuo. The residue was diluted with 6 N NaOH (200 mL), water (100 mL), and dichloromethane (300 mL) and stirred at room temperature. The mixture was filtered through filter paper to remove small amounts of undissolved solid and the biphasic mixture was transferred to a separatory funnel. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a gummy orange solid. The solid was triturated with warm hexanes, filtered, and dried in a Buchner funnel to give the title compound (3.03 g, 62%) as a tan solid. $MS(ES)^+$ m/e 375 [2M+H].

c) *N*-(5-bromo-2-methyl-3-pyridinyl)methanesulfonamide

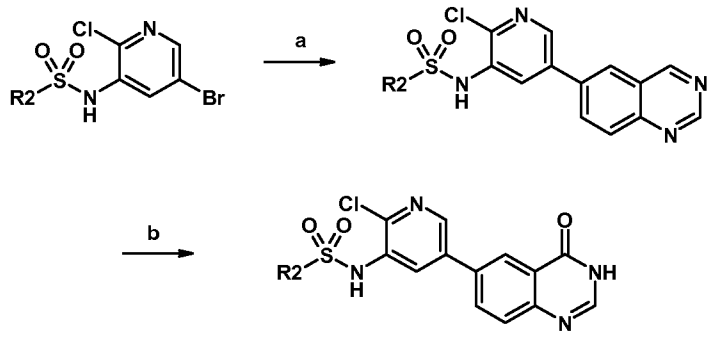
A mixture of 5-bromo-2-methyl-3-pyridinamine (0.800 g, 4.28 mmol) and triethylamine (1.731 g, 17.11 mmol) in dichloromethane (20 mL) was cooled to 0 °C and to this was added a solution of methanesulfonyl chloride (1.960 g, 17.11 mmol) in dichloromethane (8 mL). The ice bath was removed and the reaction was stirred for 1 hour. The dichloromethane was removed in vacuo and the residue was diluted with methanol (20 mL) and 10% aqueous NaOH (6.2 mL) and stirred for 2 hours at room temperature. The methanol was removed in vacuo and the residue was triturated with water and dried overnight in a Buchner funnel to give the title compound (0.614 g, 54.1%) as a tan solid. $MS(ES)^+$ m/e 264.8 [M+H].

d) *N*-[2-methyl-5-(6-quinolinyl)-3-pyridinyl]methanesulfonamide

A mixture of *N*-(5-bromo-2-methyl-3-pyridinyl)methanesulfonamide (0.172 g, 0.649 mmol), 6-quinolinylboronic acid (0.112 g, 0.649 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.026 g, 0.032 mmol), and 2 M aqueous potassium carbonate (0.359 g, 2.59 mmol) in 1,4-dioxane (6.5 mL) was heated at reflux for 3 hours and concentrated in vacuo. The residue was purified by chromatography on silica gel (7-8% MeOH:methylene chloride) to give a tan solid which was then purified by chromatography on silica

gel (7% MeOH:methylene chloride) to give the title compound (0.0327 g, 16%) as a tan solid. MS(ES)$^+$ m/e 313.9 [M+H].

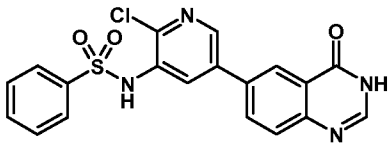
Scheme 9:



Conditions: a) bis(pinacolato)diboron, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, potassium acetate, dioxane, heat; then 6-bromoquinazoline, 2 M aqueous sodium carbonate, heat; b) 30% aqueous hydrogen peroxide, glacial acetic acid, heat.

Example 67

N-[2-Chloro-5-(4-oxo-1,4-dihydro-6-quinazolinyl)-3-pyridinyl]benzenesulfonamide



a) *N*-[2-chloro-5-(6-quinazolinyl)-3-pyridinyl]benzenesulfonamide

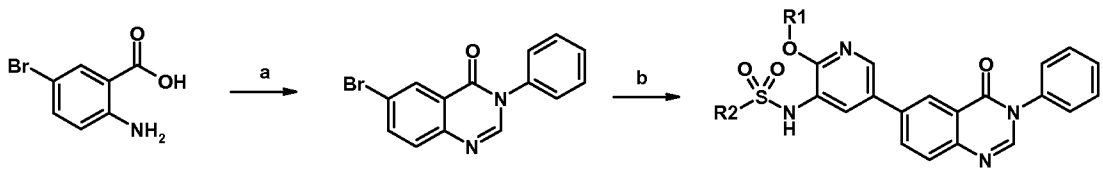
A slurry of N-(5-bromo-2-chloro-3-pyridinyl)benzenesulfonamide (493 mg, 1.418 mmol), bis(pinacolato)diboron (375 mg, 1.477 mmol), potassium acetate (232 mg, 2.363 mmol) and $PdCl_2(dppf)$-CH_2Cl_2 (48.2 mg, 0.059 mmol) in anhydrous 1,4-dioxane (9.60 mL) was heated at 100 °C for 6 h. The reaction was cooled slightly then treated with 6-bromoquinazoline (247 mg, 1.182 mmol), 2 M aqueous sodium carbonate (2.363 mL, 4.73 mmol) and another portion of $PdCl_2(dppf)$-CH_2Cl_2 (48.2 mg, 0.059 mmol) then heated at 100 °C for a further 20 h. The reaction was cooled to room temperature then concentrated under reduced pressure. The resulting crude residue was slurried in ethyl acetate then treated with decolorizing charcoal and

anhydrous sodium sulfate. Filtered through a short pad of silica then the filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography with 40% hexanes in ethyl acetate. The combined, desired fractions were evaporated to give the product (236 mg, 49.8%) as a white solid. MS(ES)+ m/e 396.7 $[M+H]^+$. 1H NMR (400 MHz, DMSO-*d*6) δ ppm 7.60 (t, *J*=7.58 Hz, 3 H) 7.66 - 7.74 (m, 1 H) 7.78 (d, *J*=7.07 Hz, 2 H) 7.77 (s, 1 H) 8.12 - 8.21 (m, 3 H) 8.34 (dd, *J*=8.84, 2.27 Hz, 1 H) 8.51 (d, *J*=2.02 Hz, 1 H) 8.76 (d, *J*=2.27 Hz, 1 H) 9.36 (s, 1 H) 9.70 (s, 1 H) 10.54 (s, 1 H).

b) *N*-[2-chloro-5-(4-oxo-1,4-dihydro-6-quinazolinyl)-3-pyridinyl]benzenesulfonamide

A slurry of N-[2-chloro-5-(6-quinazolinyl)-3-pyridinyl]benzenesulfonamide (223 mg, 0.562 mmol) in glacial acetic acid (5.0 mL, 87 mmol) was treated with 30% aqueous hydrogen peroxide (2.0 mL, 19.58 mmol) then heated at 55 °C. After a few minutes, a clear solution resulted. Stirring continued for a further 3 hours to give a yellow slurry. The reaction was cooled to room temperature then evaporated under reduced pressure. The crude product was purified by column chromatography on silica (5% methanol in dichloromethane). The combined desired fractions were evaporated under reduced pressure and the resulting white residue was recrystallized from absolute ethanol to give the product (142 mg, 60.6%) as colorless crystals. MS(ES)+ m/e 413.0, 415.1 $[M+H]^+$ (chlorine pattern). 1H NMR (400 MHz, DMSO-*d*6) ppm 7.60 (t, *J*=7.58 Hz, 16 H) 7.65 - 7.73 (m, 8 H) 7.78 (dd, *J*=12.51, 8.46 Hz, 17 H) 7.76 (s, 6 H) 8.00 (d, *J*=2.53 Hz, 8 H) 8.11 (dd, *J*=8.34, 2.27 Hz, 8 H) 8.17 (s, 8 H) 8.29 (d, *J*=2.27 Hz, 8 H) 8.68 (d, *J*=2.27 Hz, 8 H) 10.49 (br. s., 7 H) 12.42 (br. s., 7H).

Scheme 10:

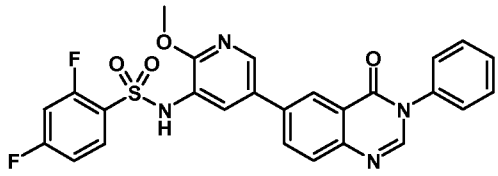


Conditions: a) triethyl orthoformate, acetic acid, heat; b) bis(pinacolato)diboron, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane

adduct, potassium acetate, dioxane, heat; then N-(5-bromo-2-alkoxy(**R1**)-3-pyridinyl) (**R2**)sulfonamide, 2 M aqueous sodium carbonate, heat.

Example 68

2,4-Difluoro-N-[2-(methyloxy)-5-(4-oxo-3-phenyl-3,4-dihydro-6-quinazolinyl)-3-pyridinyl]benzenesulfonamide



a) 6-bromo-3-phenyl-4(*3H*)-quinazolinone

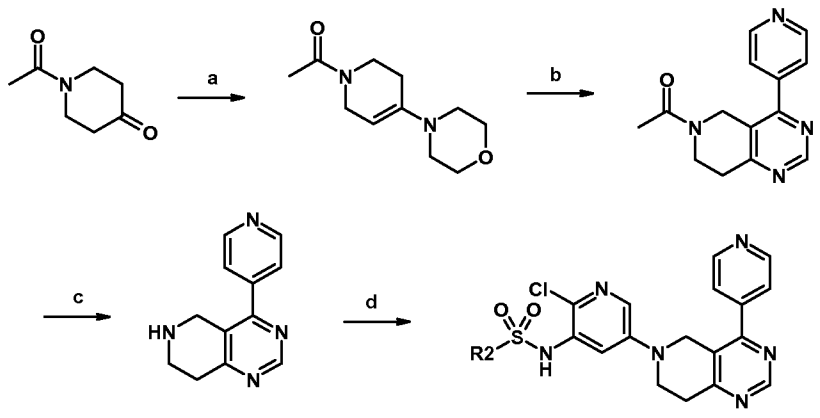
A slurry of 2-amino-5-bromobenzoic acid (1.0 g, 4.63 mmol) in toluene (25 mL) was treated with triethyl orthoformate (1.156 mL, 6.94 mmol) and acetic acid (26 µl, 0.454 mmol) then heated at reflux for 2.5 hours. The resulting clear solution was treated with neat aniline (422 µl, 4.63 mmol) and heating continued at reflux for 20 hours. The resulting slurry was cooled to room temperature then filtered. The solids were rinsed with toluene then dried under suction. The solids were purified by sililca chromatography (30% hexanes in ethyl acetate). The desired fractions were combined and evaporated under reduced pressure to give the title compound (334 g, 24%) as a white solid. MS(ES)+ m/e 300.9. 303.0 $[M+H]^+$ (bromine pattern). 1H NMR (400 MHz, DMSO-*d6*) δ ppm 7.47 - 7.62 (m, 5 H) 7.71 (d, *J*=8.59 Hz, 1 H) 8.04 (dd, *J*=8.72, 2.40 Hz, 1 H) 8.28 (d, *J*=2.27 Hz, 1 H) 8.40 (s, 1 H).

b) 2,4-difluoro-*N*-[2-(methyloxy)-5-(4-oxo-3-phenyl-3,4-dihydro-6-quinazolinyl)-3-pyridinyl]benzenesulfonamide

A slurry of 6-bromo-3-phenyl-4(3H)-quinazolinone (192 mg, 0.638 mmol), bis(pinacolato)diboron (178 mg, 0.701 mmol) , $PdCl_2(dppf)$-CH_2Cl_2 (26.0 mg, 0.032 mmol) and potassium acetate (125 mg, 1.275 mmol) in anhydrous 1,4-dioxane (5.20 mL) was heated at 100 °C for 3 h. The reaction was then treated with N-[5-bromo-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (254 mg, 0.669 mmol), 2 M aqueous sodium carbonate (1.275 mL, 2.55 mmol) and another portion of

$PdCl_2(dppf)$-CH_2Cl_2 (26.0 mg, 0.032 mmol) then heated at 100 °C for a further 20 h. The reaction was cooled to room temperature then concentrated under reduced pressure. The resulting crude residue was slurried in ethyl acetate then treated with decolorizing charcoal and anhydrous sodium sulfate. Filtered through a short pad of silica then the filtrate was evaporated under reduced pressure. The resulting residue was purified by prep-HPLC using acetonitrile/water-0.1% TFA as mobile phase (10-90% aqueous gradient). The combined desired fractions were treated with saturated aqueous sodium bicarbonate (2 mL) then concentrated under reduced pressure only to remove volatile organics. The resulting slurry was extracted with ethyl acetate then the extracts were dried over anhydrous sodium sulfate. Evaporation of the filtered solution afforded a colorless oil that was crystallized from hot ethyl acetate/hexanes to give the product (63 mg, 19%) as a white solid. MS(ES)+ m/e 521.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-*d*6) δ ppm 3.68 (s, 16 H) 7.22 (d, *J*=2.02 Hz, 6 H) 7.48 - 7.64 (m, 34 H) 7.72 - 7.82 (m, 6 H) 7.84 (d, *J*=8.59 Hz, 6 H) 7.97 (d, *J*=2.27 Hz, 6 H) 8.16 (dd, *J*=8.46, 2.15 Hz, 6 H) 8.32 (d, *J*=2.02 Hz, 6 H) 8.39 (s, 5 H) 8.45 (d, *J*=2.27 Hz, 5 H) 10.37 (s, 5 H).

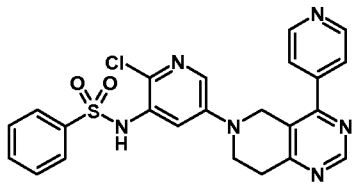
Scheme 11:



Conditions: a) morpholine, p-toluenesulfonic acid monohydrate, benzene, reflux; b) isonicotinyl chloride hydrochloride salt, triethylamine, methylene chloride, 0 °C to room temperature; then formamidine acetic acid salt, ethanol, reflux; c) 3 N hydrochloric acid, heat; d) N-(5-bromo-2-chloro-3-pyridinyl) (**R2**)sulfonamide, sodium t-butoxide, palladium(II) acetate, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, toluene, t-BuOH, heat.

Example 69

N-{2-Chloro-5-[4-(4-pyridinyl)-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl]-3-pyridinyl}benzenesulfonamide



a) 4-(1-acetyl-1,2,3,6-tetrahydro-4-pyridinyl)morpholine

To 1-acetyl-4-piperidinone (20 g, 141 mmol) in benzene (300 mL) was added morpholine (14 mL, 160 mmol) and p-toluenesulfonic acid mono hydrate (200 mg, 1.0 mmol). The reaction was stirred and heated at reflux with a Dean-Stark trap (100 °C oil bath) to collect generated water (~2.6 mL). After 18 h refluxing the reaction was cooled and evaporated to dryness under vacuum to give the title product (32.4 g, 156 mmol) as a thick yellow oil. Note: LCMS was not useable since the product was unstable to the column conditions. This material was used as is in the next reaction.

b) 6-acetyl-4-(4-pyridinyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a stirred solution of 1-acetyl-4-(1-piperidinyl)-1,2,3,6-tetrahydropyridine (32.4 g, 156 mmol) in CH_2Cl_2 (400 mL) at 0 °C was added Et_3N (44 mL, 316 mmol) and isonicotinyl chloride HCl salt (28 g, 198 mmol). The reaction was allowed to warm to RT and stirred for 18 h. The reaction was evaporated to dryness, taken up in EtOAc (200 mL), filtered free of insoluble solids, evaporated and taken up in ethanol (300 mL). To the stirred solution was added formamidine HOAc salt (20 g, 454 mmol) and the reaction heated at reflux for 18 h. After cooling to RT the reaction was evaporated to dryness and purified by flash chromatography on silica gel (0 to 10% MeOH in CH_2Cl_2) to give the uncyclized (1-acetyl-4-amino-1,2,5,6-tetrahydro-3-pyridinyl)(4-pyridinyl)methanone after evaporation to dryness under vacuum. This material was taken up in formamide (100 mL, 2.5 mol) and formic acid (10 mL, 256 mmol) and heated at reflux for 24 h. (A majority of the material was cyclized to the desired product by LCMS.) The reaction was concentrated under vacuum with heating, basified with 1 N Na_2CO_3,

extracted with 10% iPrOH in CH_2Cl_2, dried (Na_2SO_4), filtered and evaporated to dryness. Purification by flash chromatography on silica gel (0 to 10% MeOH in CH_2Cl_2) followed by trituration with (1:1) Et_2O, Pet. Ether, filtration and drying under vacuum gave the title product (6.05 g, 23.7 mmol, 15.3 % yield) as a beige solid. LCMS MS(ES)+ m/e 255.1 $[M+H]^+$.

c) 4-(4-pyridinyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

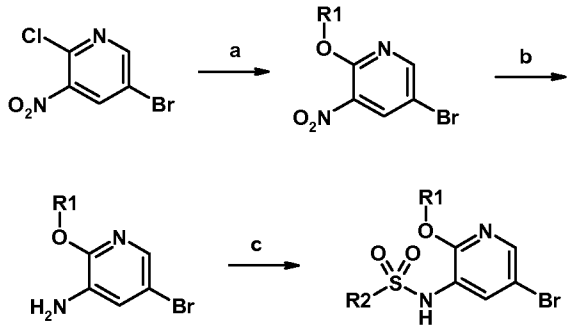
To 6-acetyl-4-(4-pyridinyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (4.0 g, 15.73 mmol) was added aq. 3 N HCl (50 mL, 150 mmol). The reaction was stirred and heated at 80 °C for 6 h. The reaction was cooled to RT and evaporated to dryness under vacuum. The crude HCl salt was neutralized with aq. 1 N NaOH to pH~9 and evaporated to dryness under vacuum. Purification by flash chromatography on silica gel (10 to 15% (5% NH_4OH/MeOH) in CH_2Cl_2) gave the title product (2.05 g, 9.6 mmol, 61.4 % yield) as an off-white solid. A second less pure fraction was also obtained (0.67 g, 80 to 90% pure by TLC). LCMS MS(ES)+ m/e 212.7 $[M+H]^+$.

d) *N*-{2-chloro-5-[4-(4-pyridinyl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl]-3-pyridinyl}benzenesulfonamide

In a glass pressure vessel was added N-(5-bromo-2-chloro-3-pyridinyl)benzenesulfonamide (0.7 g, 2.0 mmol), 4-(4-pyridinyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.5 g, 2.3 mmol), sodium t-butoxide (0.4 g, 4.1 mmol), $Pd(OAc)_2$ (50 mg, 0.22 mmol), X-Phos (110 mg, 0.23 mmol) and (5:1) toluene, t-BuOH (15 mL) . The reaction was purged with N_2, capped and stirred at 120 °C for 18 h. After cooling to RT the reaction was neutralized with aq. 6 N HCl (0.7 mL, 4.2 mmol) transfered to a round bottom flask and evaporated to dryness under vacuum. The crude material was purified by flash chromatography on silica gel (5 to 15% MeOH in CH_2Cl_2) (discarded ~15% product that contained a lower impurity), triturated with (1:1) ether/pet. ether, filtered, and dried under vacuum to give the title product (124 mg, 0.25 mmol, 10.9 % yield) as a yellow solid. LCMS MS(ES)+ m/e 479.0 $[M+H]^+$.

Additional Intermediates:

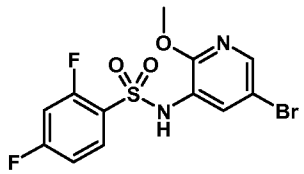
Scheme 12:



Conditions: a) sodium methoxide (or **R1**-ONa), methanol (or **R1**-OH), 0 °C; b) tin(II)chloride dihydrate, ethyl acetate, reflux; c) **R2**-SO_2Cl, pyridine (or **R2**-SO_2Cl, triethylamine, methylene chloride).

Intermediate 1

N-[5-Bromo-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide



a) 5-bromo-2-(methyloxy)-3-nitropyridine

To a cooled (0 °C) solution of 5-bromo-2-chloro-3-nitropyridine (50 g, 211 mmol) in methanol (200 mL) was added dropwise over 10 minutes 20% sodium methoxide (50 mL, 211 mmol) solution. The reaction, which quickly became heterogeneous, was allowed to warm to ambient temperature and stirred for 16 h. The reaction was filtered and the precipitate diluted with water (200 mL) and stirred for 1 h. The solids were filtered, washed with water (3 x 100 mL) and dried in a vac oven (40 °C) to give 5-bromo-2-(methyloxy)-3-nitropyridine (36 g, 154 mmol, 73.4 % yield) as a pale yellow powder. The original filtrate was concentrated in vacuo and diluted with water (150 mL). Saturated ammonium chloride (25 mL) was added and the mixture stirred for 1 h. The solids were filtered, washed with water, and

dried in a vac oven (40 °C) to give a second crop of 5-bromo-2-(methyloxy)-3-nitropyridine (9 g, 38.6 mmol, 18.34 % yield). Total yield = 90%. MS(ES)+ m/e 232.8, 234.7 $[M+H]^+$.

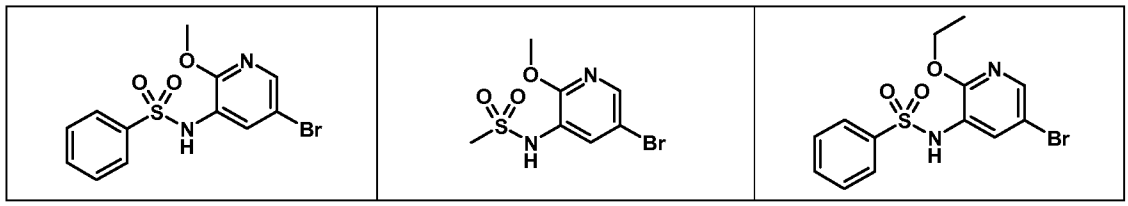
b) 5-bromo-2-(methyloxy)-3-pyridinamine

To a solution of 5-bromo-2-(methyloxy)-3-nitropyridine (45 g, 193 mmol) in ethyl acetate (1 L) was added tin(II) chloride dihydrate (174 g, 772 mmol). The reaction mixture was heated at reflux for 4 h. LC/MS indicated some starting material remained, so added 20 mol% tin (II) chloride dihydrate and continued to heat at reflux. After 2 h, the reaction was allowed to cool to ambient temperature and concentrated in vacuo. The residue was treated with 2 N sodium hydroxide and the mixture stirred for 1 h. The mixture was then with methylene chloride (1 L), filtered through Celite, and washed with methylene chloride (500 mL). The layers were separated and the organics dried over magnesium sulfate and concentrated to give 5-bromo-2-(methyloxy)-3-pyridinamine (23 g, 113 mmol, 58.7 % yield). The product was used crude in subsequent reactions. MS(ES)+ m/e 201.9, 203.9 $[M+H]^+$.

c) *N*-[5-bromo-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

To a cooled (0 °C) solution of 5-bromo-2-(methyloxy)-3-pyridinamine (20.3 g, 100 mmol) in pyridine (200 mL) was added slowly 2,4-difluorobenzenesulfonyl chloride (21.3 g, 100 mmol) over 15 min (reaction became heterogeneous). The ice bath was removed and the reaction was stirred at ambient temperature for 16 h, at which time the reaction was diluted with water (500 mL) and the solids filtered off and washed with copious amounts of water. The precipitate was dried in a vacuum oven at 50 °C to give N-[5-bromo-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (12 g, 31.6 mmol, 31.7 % yield) MS(ES)+ m/e 379.0, 380.9 $[M+H]^+$.

*Other N-[5-bromo-2-(alkoxy)-3-pyridinyl]sulfonamides were or can be prepared using this procedure by varying the choice of sulfonyl chloride and alkoxide.



Exemplary capsule composition

An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table II, below.

Table II

INGREDIENTS	AMOUNTS
Compound of example 1	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Exemplary Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.5% by weight of compound of example 1 in 10% by volume propylene glycol in water.

Exemplary Tablet Composition

The sucrose, calcium sulfate dihydrate and an PI3K inhibitor as shown in Table III below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid;, screened and compressed into a tablet.

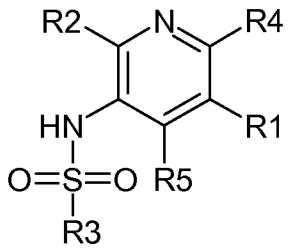
Table III

INGREDIENTS	AMOUNTS
Compound of example 1	20 mg
calcium sulfate dehydrate	30 mg
Sucrose	4 mg
Starch	2 mg
Talc	1 mg
stearic acid	0.5 mg

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A method of treating cancer in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I)(D):



(I)(D)

, or a pharmaceutically acceptable salt thereof, in which

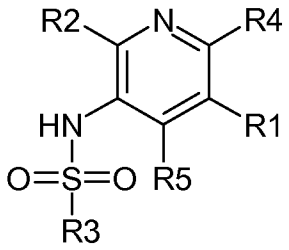
R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, unsubstituted heteroaryl, and substituted heteroaryl,

wherein the substituted heteroaryl is selected from the group consisting of: pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl;

R2 is selected from the group consisting of: hydroxyl, aminocarbonyl, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, cyano, alkoxy, nitro and acyloxy; and

R3, R4 and R5 are independently selected from the group consisting of: hydroxyl, hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, cyano, alkoxy, nitro, acyloxy, and aryloxy.

2. A compound of of claim 1 represented by Formula (I)(E):



(I)(E)

, or a pharmaceutically acceptable salt thereof, in which

R1 is a cyclic ring selected from the group consisting of: C3-12cycloalkyl, substituted C3-12cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, unsubstituted heteroaryl, and substituted heteroaryl,

wherein the substituted heteroaryl is selected from the group consisting of: quinazolinonyl, tetrahydropyridoprimidinyl, pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl;

R2 is selected from the group consisting of: aminocarbonyl, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, cyano, alkoxy, nitro and acyloxy;

R3 is selected from the group consisting of: amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, alkoxy, and aryloxy;

R4 and R5 are each independently selected from the group consisting of: hydrogen, halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, cyano, alkoxy, nitro and acyloxy.

3. A compound of claim 2 wherein

R1 is selected from the group consisting of: aryl, substituted aryl, unsubstituted heteroaryl, and substituted heteroaryl, wherein the substituted heteroaryl is selected from the group consisting of: quinazolinonyl, tetrahydropyridoprimidinyl, pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl;

R2 is selected from: cyano, substitituted amino, halogen, C1-6alkyl, amino, alkoxy and cyclopropyl;

R3 is selected from the group consisting of: amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, arylcycloalkyl, substituted arylcycloalkyl, heteroarylalkyl, substituted heteroarylalkyl, alkoxy, and aryloxy; and

R4 and R5 are each independently selected from the group consisting of: hydrogen, halogen, acyl, amino, C1-6alkyl and cyclopropyl;
or a pharmaceutically acceptable salt thereof.

4. A compound according to any of the above claims, wherein

R2 is halogen, C1-6alkyl, substituted C1-6alkyl, alkoxy or cyclopropyl; and

R3 is C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, aryl which is optionally substituted with one to three groups selected from: halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, cyano, alkoxy, nitro, acyloxy, and aryloxy, wherein two adjacent substituents may form an additional 5 or 6-membered non-aromatic ring containing zero to three heteroatoms, or heteroaryl which is optionally substituted with one to three groups selected from: halogen, acyl, amino, substituted amino, C1-6alkyl,

substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, cyano, alkoxy, nitro, acyloxy, and aryloxy

5. A compound according to any one of the above claims wherein R1 is phenyl or substituted phenyl; or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of the above claims, wherein R1 is unsubstituted heteroaryl or substituted heteroaryl, wherein the substituted heteroaryl is selected from the group consisting of: quinazolinonyl, tetrahydropyridoprimidinyl, pyridinyl, primidinyl, benzothiazolyl, benzimidazolyl, imidazolyl, pyrazolyl and benzopyrazolyl; the unsubstituted heteroaryl is selected from: quinoxalinyl, pyridioprimidinyl, naphthyridinyl, quinolinyl and quinazolinyl.

7. A compound according to any one of the above claims wherein R2 is alkoxy, C1-6alkyl, substituted C1-6alkyl, cyano, amino or halogen; or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of the above claims wherein R2 is methoxy, halogen, ethoxy, methyl, ethyl, trifluoromethyl, cyano or amino.

9. A compound according to any of the above claims wherein R3 is aryl optionally substituted with one to three groups selected from: halogen, acyl, amino, substituted amino, C1-6alkyl, substituted C1-6alkyl, C3-7cycloalkyl, substituted C3-7cycloalkyl, C3-7heterocycloalkyl, substituted C3-7heterocycloalkyl, alkylcarboxy, arylamino, alkoxy, and aryloxy, wherein two adjacent substituents may form an additional 5 or 6-membered non-aromatic ring containing zero to three heteroatoms; or a pharmaceutically acceptable salt thereof.

10. A compound according to any of the above claims wherein R4 and R5 are each independently selected from the group consisting of: hydrogen, halogen, cyano, amino, C1-6alkyl and cyclopropyl; or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to any one of claim 2 to 9 and a pharmaceutically acceptable carrier.

12. A method of inhibiting one or more phosphatoinositides 3-kinases (PI3Ks) in a human; comprising administering to the human a therapeutically effective amount of a compound of Formula (I)(D) or a pharmaceutically acceptable salt thereof as defined in any one of claim 1 to 9.

13. A method of treating one or more disease states selected from agroup consisting of: autoimmune disorders, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, allergy, asthma, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection and lung injuries, in a human, which method comprises administering to such human, a therapeutically effective amount of a compound according to claim 3.

14. A method of treating cancer comprises co-administration a compound according to claim 1; or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof; and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

15. A method of claim 8, wherein the disease state is selected from the group consisting of: multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, lung inflammation, thrombosis, brain infection/inflammation, meningitis and encephalitis.

16. A method of claim 12 wherein the disease is cancer.

17. A method of claim 15 wherein the cancer is selected from the group consisting of: brain (gliomas), glioblastomas, leukemias, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, renal, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

18. A method of claim 15 wherein the disease is selected from the group consisting of: ovarian cancer, pancreatic cancer, breast cancer, prostate cancer renal cancer and leukemia.

19. A method of claim 11, wherein said PI3 kinase is a PI3α.

20. A method of claim 11, wherein said PI3 kinase is a PI3γ.

21. A method of claim 15 wherein the compound is defined according to claim 2, or a pharmaceutically acceptable salt thereof, is administered in a pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80701

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 41/06; A61K 31/18 (2008.04)
USPC - 514/601
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)
USPC - 514/601

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/117, 264.1, 603 (text search - see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB); Google Patent/Scholar
Search terms used: pyridinyl, sulfonamide, benzenesulfonamide, phosphoinositide, phosphatidylinositol, kinase, PI3 kinase, inhibitor, cancer, combination chemotherapy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	WO 2007/067875 A2 (GOODMAN et al.) 14 June 2007 (14.06.2007) pg 1, ln 10-18, ln 25-31; pg 2, ln 1-26; pg 3, ln 1-4	1-4, 13 ---------- 14
Y	US 6,559,139 B1 (JOHNSON et al.) 6 May 2003 (06.05.2003) col 3, ln 21-25; col 6, ln 14-25	14

☐ 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	Date of mailing of the international search report
04 December 2008 (04.12.2008)	29 DEC 2008
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	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80701

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.: 5-12 and 15-21
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.