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(54) Title: COMPOUNDS

(57) Abstract: Invented are novel azaindole compounds, the use of such compounds as inhibitors of protein kinase B activity and in the treatment of cancer and arthritis.



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COMPOUNDS

FIELD OF THE INVENTION

- 5 This invention relates to novel azaindole compounds, the use of such compounds as inhibitors of protein kinase B (hereinafter PKB/Akt, PKB or Akt) activity and in medicine, for example for treatment of cancer or arthritis.

BACKGROUND OF THE INVENTION

- 10 Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as
15 Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science*, 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science*,
20 281:1312-1316 (1998)).

- The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548
25 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al., *Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol
30 (3,4,5)-triphosphate (PtdIns (3,4,5)-P₃), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings *Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB
35 mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997,
40 Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed
5 in breast and prostate cancer cell lines (Nakatani *et al. J. Biol.Chem.* 274:21528-21532 (1999)). It was demonstrated that Akt-2 was over-expressed in 12% of ovarian carcinomas and that amplification of Akt was especially frequent in 50% of undifferentiated tumors, suggestion that Akt may also be associated with tumor aggressiveness (Bellacosa, *et al., Int. J. Cancer*, 64, pp. 280-285, 1995). Increased
10 Akt1 kinase activity has been reported in breast, ovarian and prostate cancers (Sun *et al. Am. J. Pathol.* 159: 431-7 (2001)).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P₃, is a negative regulator of the
15 PI3K/Akt pathway (Li *et al. Science* 275:1943-1947 (1997), Stambolic *et al. Cell* 95:29-39 (1998), Sun *et al. Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw *et al. Nature Genetics* 16:64-67 (1997)). PTEN is deleted in
20 a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li *et al. supra*, Guldberg *et al. Cancer Research* 57:3660-3663 (1997), Risinger *et al. Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles
25 for regulating cell survival or apoptosis in tumorigenesis.

Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKB α , Akt2/PKB β , and Akt3/PKB γ respectively. The isoforms are homologous,
30 particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The
35 current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

40

Phosphorylation of Akt1/PKB α occurs on two regulatory sites, Thr³⁰⁸ in the catalytic domain activation loop and on Ser⁴⁷³ near the carboxy terminus (D. R. Alessi *et al.* *EMBO J.* 15:6541-6551 (1996) and R. Meier *et al.* *J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKB β and Akt3/PKB γ . The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PtdIns(3,4,5)-P₃, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. The compound UCN-01 is a reported inhibitor of PDK1. *Biochem. J.* 375(2):255 (2003). Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams *et al.* *Curr. Biol.* 10:439-448 (2000).

Small molecule inhibitors of Akt are useful in the treatment of tumors, especially those with activated Akt (e.g. PTEN null tumors and tumors with ras mutations). PTEN is a critical negative regulator of Akt and its function is lost in many cancers, including breast and prostate carcinomas, glioblastomas, and several cancer syndromes including Bannayan-Zonana syndrome (Maehama, T. *et al.* *Annual Review of Biochemistry*, 70: 247 (2001)), Cowden disease (Parsons, R.; Simpson, L. *Methods in Molecular Biology (Totowa, NJ, United States)*, 222 (*Tumor Suppressor Genes, Volume 1*): 147 (2003)), and Lhermitte-Duclos disease (Backman, S. *et al.* *Current Opinion in Neurobiology*, 12(5): 516 (2002)). Akt3 is up-regulated in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer cell lines and Akt2 is over-expressed in pancreatic and ovarian carcinomas. Akt1 is amplified in gastric cancers (Staal, *Proc. Natl. Acad. Sci. USA* 84: 5034-7 (1987) and upregulated in breast cancers (Stal *et al.* *Breast Cancer Res.* 5: R37-R44 (2003)). Therefore a small molecule Akt inhibitor is expected to be useful for the treatment of these types of cancer as well as other

types of cancer. Akt inhibitors are also useful in combination with further chemotherapeutic agents.

5 The present invention relates to novel azaindole compounds that are inhibitors of the activity of the three isoforms of the serine/threonine kinase, Akt (also known as protein kinase B). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer and arthritis (Liu et al. *Current Opin. Pharmacology* 3:317-22 (2003)).

10

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt/PKB.

15

It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

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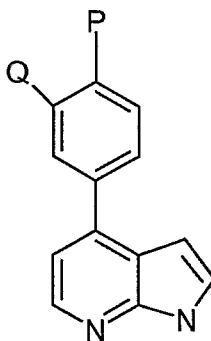
It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt/PKB activity.

It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

SUMMARY OF THE INVENTION

25

This invention relates to novel compounds of formula (I):



30

wherein:

either:

P is hydrogen and Q is -Z-R¹;

or:

Q is hydrogen and P is $-Z-R^1$;

and in either case:

5 Z is selected from the group consisting of $-SO_2-$, $-CONR^{20}-$, $-N(R^{25})CO-$, $-N(R^{25})CONR^{20}-$, $-SO_2NR^{20}-$, where R^{20} is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_6 alkoxy and halo C_1-C_6 alkyl, and R^{25} is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_6 alkoxy and halo C_1-C_6 alkyl; and

10 R^1 is C_1-C_6 alkyl or is a group $-NR^2R^3$, wherein R^2 and R^3 , together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, or R^2 is hydrogen and R^3 is selected from:

hydrogen;

tetrahydrofuranyl;

tetrahydropyranyl;

15 $-Y-NR^4R^5$, where Y is selected from $-(CH_2)_p-$, $-(CH_2)_pCHR^6-$, $-CHR^6(CH_2)_p-$, $-C_1-6alkoxyC_1-6alkyl-$ and $-(CH_2)_pSO_2-$, where p is 1, 2 or 3, R^6 is phenyl, and R^4 and R^5 are independently selected from hydrogen and $C_1-6alkyl$, or R^4 and R^5 taken together with the nitrogen to which they are attached form a morpholinyl or a piperazinyl group, the morpholinyl or piperazinyl group being optionally substituted by $C_1-6alkyl$; or R^4 is hydrogen and R^5 is selected from $C_1-6alkylsulphonyl$, phenyl and phenylsulfonyl, the phenyl and the phenyl moiety in the phenylsulfonyl group being optionally substituted by $C_1-6alkyl$; and

20 $-(CH_2)_m-X$ wherein m is 0, 1 or 2 and X is selected from phenyl, phenyl substituted with from one to three substituents selected from $-C_1-6alkyl$, $-C_1-6alkoxy$ and sulfamoyl, thiocyclopentane-1,1-dioxide, thiocyclohexane-1,1-dioxide and indolyl;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

30 By the term " C_1-C_6 alkyl", " $C_1-6alkyl$ " and derivatives thereof as used herein, as a group or a part of a group, is meant a linear or branched, saturated or unsaturated hydrocarbon chain containing from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl, hexyl, $-CH=CH_2$, and $-C\equiv C-CH_3$.

By the term " C_1-C_6 alkoxy", " $C_1-6alkoxy$ " and derivatives thereof as used herein is meant the group $-O-C_1-6alkyl$, wherein $C_1-6alkyl$ is as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

The term "C₁₋₆alkylsulfonyl" refers to the group C₁₋₆alkyl-SO₂-. Similarly, the term "phenylsulfonyl" refers to a group phenyl-SO₂-.

In one embodiment, R¹ is methyl, a pyrrolidinyl ring or -NH₂.

5

In one embodiment, R₁ is a group -NR₂R₃, wherein R₂ is hydrogen and R₃ is:

- tetrahydrofuranyl; or
- tetrahydropyranyl; or
- 10 • a group -(CH₂)_m-X wherein m is 0 or 1 or 2 and X is phenyl (optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy or sulfamoyl), thiocyclopentane-1,1-dioxide, thiocyclohexane-1,1-dioxide or indolyl; or
- 15 • a group -(CH₂)_pNR₄R₅, wherein p is 1, 2 or 3, R₄ and R₅ are independently hydrogen or C₁₋₆alkyl, or R₄ and R₅ form a morpholinyl or a piperazinyl group, the morpholinyl or a piperazinyl group being optionally substituted by C₁₋₆alkyl; or R₄ is hydrogen and R₅ is C₁₋₆alkylsulphonyl or phenylsulfonyl, the phenyl moiety in the phenylsulfonyl group being optionally substituted by C₁₋₆alkyl; or
- 20 • a group -(CH₂)_pCHR₆NR₄R₅ or -CHR₆(CH₂)_pNR₄R₅, p is 1 or 2, R₆ is phenyl, R₄ and R₅ are independently hydrogen or C₁₋₆alkyl, or R₄ and R₅ form a morpholinyl or a piperazinyl group, the morpholinyl or a piperazinyl group being optionally substituted by C₁₋₆alkyl; or
- a group -C₁₋₆alkoxyC₁₋₆alkyl-NR₄R₅, wherein R₄ and R₅ are independently hydrogen or C₁₋₆alkyl; or
- 25 • a group -(CH₂)_pSO₂NR₄R₅, wherein p is 2 or 3, R₄ and R₅ are independently hydrogen or C₁₋₆alkyl, or R₄ is hydrogen and R₅ is phenyl, the phenyl being optionally substituted by C₁₋₆alkyl, or R₄ and R₅ form a piperazinyl group, the piperazinyl group being optionally substituted by C₁₋₆alkyl.

In one embodiment, R₁ is a group -NR₂R₃, wherein R₂ is hydrogen and R₃ is:

- 30 • tetrahydrofuranyl; or
- tetrahydropyranyl; or
- a group -(CH₂)_m-X wherein m is 0 or 1 or 2 and X is phenyl (optionally substituted by methoxy or sulfamoyl), thiocyclopentane-1,1-dioxide, thiocyclohexane-1,1-dioxide or indolyl; or
- 35 • a group -(CH₂)_pNR₄R₅, wherein p is 1, 2 or 3, R₄ and R₅ are independently hydrogen, methyl or ethyl, or R₄ and R₅ form a morpholinyl or a piperazinyl group, the morpholinyl or a piperazinyl group being optionally substituted by methyl or ethyl; or R₄ is hydrogen and R₅ is C₁₋₆alkylsulphonyl or phenylsulfonyl, the phenyl moiety in the phenylsulfonyl group being
- 40 optionally substituted by methyl or ethyl; or

- a group $-(CH_2)_pCHR_6NR_4R_5$ or $-CHR_6(CH_2)_pNR_4R_5$, p is 1 or 2, R_6 is phenyl, R_4 and R_5 are independently hydrogen or methyl, or R_4 and R_5 form a morpholinyl group, optionally substituted by methyl or ethyl; or
- a group $-(CH_2)_qO(CH_2)_qNR_4R_5$, wherein q is independently 2 or 3 and R_4 and R_5 are independently hydrogen, methyl or ethyl; or
- a group $-(CH_2)_pSO_2NR_4R_5$, wherein p is 2 or 3, R_4 and R_5 are independently hydrogen, methyl or ethyl, or R_4 is hydrogen and R_5 is phenyl, the phenyl being optionally substituted by methyl or ethyl, or R_4 and R_5 form a piperazinyl group, the piperazinyl group being optionally substituted by methyl or ethyl.

Included among the compounds of the present invention are:

- N*-{[3-(methyloxy)phenyl]methyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[2-(4-morpholinyl)-1-phenylethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[2-(dimethylamino)-2-phenylethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-phenyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[2-(dimethylamino)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[3-(dimethylamino)propyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[2-(4-morpholinyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-(2-aminoethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-(3-{[2-(dimethylamino)ethyl]oxy}propyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-{2-[4-(aminosulfonyl)phenyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[2-(1*H*-indol-2-yl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[2-(1-piperazinyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- 4-[4-(1-Pyrrolidinylsulfonyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine;
- 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- 4-[4-(Methylsulfonyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine;
- N*-[2-(methylsulfonyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-[(1,1-dioxidotetrahydro-3-thienyl)methyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-(1,1-dioxidotetrahydro-3-thienyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N*-{3-[(methylsulfonyl)amino]propyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;

- N -[2-(aminosulfonyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 4-methyl- N -[2-({[4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)phenyl]sulfonyl}amino)ethyl]benzenesulfonamide;
 N -[3-(aminosulfonyl)propyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 5 N -{2-[(methylamino)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 N -{2-[(dimethylamino)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 N -{2-[(4-methyl-1-piperazinyl)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 10 N -{2-[(phenylamino)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 N -{2-[(ethylamino)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 15 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)- N -(tetrahydro-2*H*-pyran-4-yl)benzenesulfonamide;
 and
 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)- N -[(3*S*)-tetrahydro-3-furanyl]benzenesulfonamide;

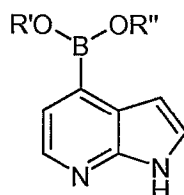
and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

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In another aspect, the present invention provides a method of manufacturing a compound of formula (I) as defined above, comprising:

(a) reacting a compound of formula (II):

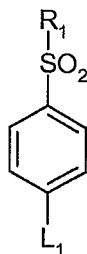
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(II)

wherein R' and R'' are independently hydrogen or C₁₋₆alkyl, or R' and R'' form a 5 or 6 membered ring optionally substituted by 1 to 4 C₁₋₆alkyl groups; with a compound of formula (III):

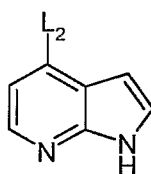
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(III)

wherein R_1 is as defined for formula (I) and L_1 is a leaving group; or

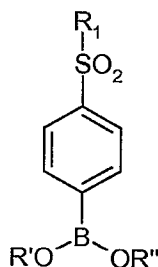
- 5 (b) reacting a compound of formula (IV):



(IV)

wherein L_2 is a leaving group, with a compound of formula (V):

10



(V)

- 15 wherein R_1 is as defined for formula (I), R' and R'' are independently hydrogen or C_{1-6} alkyl or R' and R'' form a 5 or 6 membered ring optionally substituted by 1 to 4 C_{1-6} alkyl groups;

and thereafter optionally for process (a) or process (b):

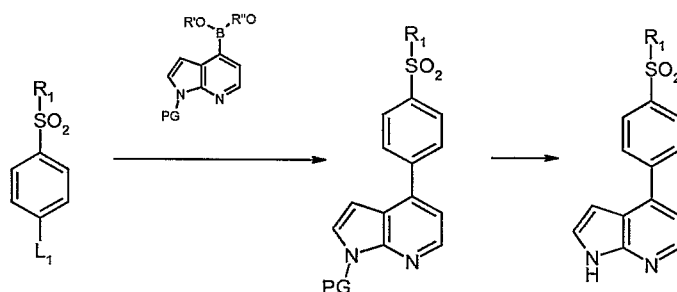
- 20
- removing any protecting groups;
 - forming a pharmaceutically acceptable salt;
 - converting a compound of formula (I) to another compound of formula (I).

In the above processes, SO_2 can be replaced by another linker such as Z as defined in figure 1.

In processes (a) and (b), the leaving groups L_1 and L_2 may be any suitable leaving group, such as halogen (eg Br, Cl or I) or -OTf.

- 5 In processes (a) and (b), the group $-B(OR')(OR'')$ may be any suitable boronate group, for example 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl.

It will be appreciated that the final step in preparing a compound of formula (I) may in fact be the removal of a protecting group. For example, the NH group in the pyrrolopyridinyl moiety may be protected during the coupling reaction of process (a)
 10 by a suitable protecting group such as methylphenylsulfonyl, for example:



- 15 wherein R_1 , L_1 , R' and R'' are as defined above and PG is a protecting group. The skilled person would be aware of the appropriate reaction conditions for the removal of the particular protection group. For example, a base such as NaOH may be used if the protecting group is methylphenylsulfonyl.
- 20 It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives
 25 may therefore be described as "prodrugs". Further, certain compounds of the invention may act as prodrugs of other compounds of the invention. All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention. Examples of suitable protecting groups for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9,
 30 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of
 35 Prodrugs" (the disclosure in which document is incorporated herein by reference)

may be placed on appropriate functionalities when such functionalities are present within compounds of the invention.

5 The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed herein inhibit each of the three Akt/PKB isoforms.

10 Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

As used herein, the term "effective amount" and derivatives thereof 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" and derivatives thereof means any amount which, as compared to a corresponding
15 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.

20 Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods 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
25 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.

30 All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer,
35 including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. 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 or arthritis. Preferably, if the administration is not simultaneous, the compounds are
40 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 of 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 presently invented AKT 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 G₂/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, 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -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. Intern. 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 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -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, vincalukoblastine 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.

- 5 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 myelosuppression and
10 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.
15 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.

- 20 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
25 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
30 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
35 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
40 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.

5

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.

10

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.

15

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.

20

25

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.

30

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.

35

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

40

agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

5 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, anthracyclins such as daunorubicin and doxorubicin; and bleomycins.

10

Dactinomycin, also known 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.

15

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®.

20

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.

25

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.

30

Myelosuppression is the most common dose limiting side effect of doxorubicin.

35

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.

40

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 G₂ 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.

5 Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as
10 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.

15 Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(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
20 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
25 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.

30 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,
35 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.

40 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
5 leucopenia, thrombocytopenia, and mucositis.

10 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.

15 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
20 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.

25 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
30 pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

35 Methotrexate, N-[4[[[2,4-diamino-6-pteridiny] 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 and/or replication through the inhibition of dihydrofolic 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
40 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.

5 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-

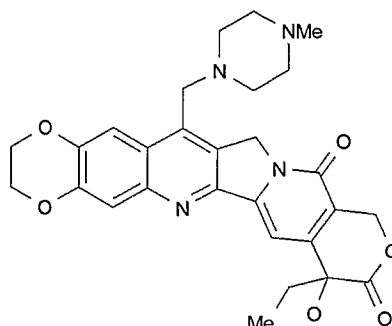
10

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®.

15 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 : irinotecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of
20 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,
25 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
30 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
35 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 and/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, letrozole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestins 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 5 α -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 as 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) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagonists 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 transduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphatidylinositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyze 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.

- 5 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.
- 10 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
- 15 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.
- 20 (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-lacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.
- Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of
- 25 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.
- 30 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,
- 35 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
- 40 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*, (1989) 1423(3):19-30.

5

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 Kinases*, *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.

5 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
10 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.

15 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
20 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.

25 In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of formula I and/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,
30 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.

35 Because the pharmaceutically active compounds of the present invention are active as AKT inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

40 Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head

and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from ovarian, pancreatic and prostate.

Isolation and Purification of His-tagged AKT1 (aa 136-480)

Insect cells expressing His-tagged AKT1 (aa 136-480) were lysed in 25 mM HEPES, 100 mM NaCl, 20 mM imidazole; pH 7.5 using a polytron (5 mLs lysis buffer/g cells). Cell debris was removed by centrifuging at 28,000 x g for 30 minutes. The supernatant was filtered through a 4.5-micron filter then loaded onto a nickel-chelating column pre-equilibrated with lysis buffer. The column was washed with 5 column volumes (CV) of lysis buffer then with 5 CV of 20% buffer B, where buffer B is 25 mM HEPES, 100 mM NaCl, 300 mM imidazole; pH 7.5. His-tagged AKT1 (aa 136-480) was eluted with a 20-100% linear gradient of buffer B over 10 CV. His-tagged AKT1 (136-480) eluting fractions were pooled and diluted 3-fold with buffer C, where buffer C is 25 mM HEPES, pH 7.5. The sample was then chromatographed over a Q-Sepharose HP column pre-equilibrated with buffer C. The column was washed with 5 CV of buffer C then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl; pH 7.5. His-tagged AKT1 (aa 136-480) containing fractions were pooled and concentrated in a 10-kDa molecular weight cutoff concentrator. His-tagged AKT1 (aa 136-480) was chromatographed over a Superdex 75 gel filtration column pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 1 mM DTT; pH 7.5. His-tagged AKT1 (aa 136-480) fractions were examined using SDS-PAGE and mass spec. The protein was pooled, concentrated and frozen at -80C.

His-tagged AKT2 (aa 138-481) and His-tagged AKT3 (aa 135-479) were isolated and purified in a similar fashion.

AKT Enzyme Assay

Compounds of the present invention were tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-

ARKRERAYSFGHHA-amide). Substrate phosphorylation was detected by the following procedure:

Assays were performed in 384well U-bottom white plates. 10 nM activated AKT enzyme was incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM MgCl₂, 4uM ATP, 8uM peptide, 0.04 uCi [γ-³³P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction was stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg²⁺ and Ca²⁺, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate was sealed, the beads were allowed to settle overnight, and then the plate was counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses were plotted as % Control calculated with the data reduction formula $100 * (U1 - C2) / (C1 - C2)$ versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: $y = (V_{max} * x) / (K + x)$ where Vmax is the upper asymptote and K is the IC50.

20

Cloning of full-length human (FL) AKT1:

Full-length human AKT1 gene was amplified by PCR from a plasmid containing myristylated-AKT1-ER (gift from Robert T. Abraham, Duke University under MTA, described in Klippel et al. in Molecular and Cellular Biology 1998 Volume 18 p.5699) using the 5' primer: 5' TATATAGGATCCATGAGCGACGTGGC 3' and the 3' primer: AAATTTCTCGAGTCAGGCCGTGCTGCTGG 3'. The 5' primer included a BamHI site and the 3' primer included an XhoI site for cloning purposes. The resultant PCR product was subcloned in pcDNA3 as a BamHI / XhoI fragment. A mutation in the sequence (TGC) coding for a Cysteine²⁵ was converted to the wild-type AKT1 sequence (CGC) coding for an Arginine²⁵ by site-directed mutagenesis using the QuikChange[®] Site Directed Mutagenesis Kit (Stratagene). The AKT1 mutagenic primer: 5' ACCTGGCGGCCACGCTACTTCCTCC and selection primer: 5' CTCGAGCATGCAACTAGAGGGCC (designed to destroy an XbaI site in the multiple cloning site of pcDNA3) were used according to manufacturer's suggestions. For expression/purification purposes, AKT1 was isolated as a BamHI / XhoI fragment and cloned into the BamHI / XhoI sites of pFastbacHTb (Invitrogen).

35

Expression of FL human AKT1:

Expression was done using the BAC-to-BAC Baculovirus Expression System from
5 Invitrogen (catalog # 10359-016). Briefly 1) the cDNA was transferred from the
FastBac vector into bacmid DNA, 2) the bacmid DNA was isolated and used to
transfect Sf9 insect cells, 3) the virus was produced in Sf9 cells, 4) T. ni cells were
infected with this virus and sent for purification.

10 Purification of FL human AKT1:

For the purification of full-length AKT1, 130 g sf9 cells (batch # 41646W02) were
resuspended in lysis buffer (buffer A, 1L, pH 7.5) containing 25 mM HEPES, 100
mM NaCl, and 20 mM imidazole. The cell lysis was carried out by Avestin (2
15 passes at 15K-20K psi). Cell debris was removed by centrifuging at 16K rpm for 1
hour and the supernatant was batch bound to 10 ml Nickel Sepharose HP beads at
4 C for over night. The beads were then transferred to column and the bound
material was eluted with buffer B (25 mM HEPES, 100 mM NaCl, 300 mM
imidazole, pH 7.5). AKT eluting fractions were pooled and diluted 3 fold using
20 buffer C (25 mM HEPES, 5 mM DTT; pH 7.5). The sample was filtered and
chromatographed over a 10 mL Q-HP column pre-equilibrated with buffer C at 2
mL/min.

The Q-HP column was washed with 3 column volume (CV) of buffer C, then step
25 eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100%
D; where buffer D is 25 mM HEPES, 1000 mM NaCl, 5 mM DTT; pH 7.5. 5 mL
fractions collected. AKT containing fractions were pooled and concentrated to 5 ml.
The protein was next loaded to a 120 ml Superdex 75 sizing column that was pre-
equilibrated with 25 mM HEPES, 200 mM NaCl, 5 mM DTT; pH 7.5. 2.5 mL
30 fractions were collected.

AKT 1 eluting fractions were pooled, aliquoted (1 ml) and stored at -80C. Mass
spec and SDS-PAGE analysis were used to confirm purity and identity of the
purified full-length AKT1.

35

Full-length (FL) AKT2 and (FL) AKT3 were isolated and purified in a similar fashion.

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

10 The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring AKT 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 demonstrated ability to act as Akt 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
15 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.
20
25

30 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.

35 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 an Akt 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
40

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.

5

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt 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.

10

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

15

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

20

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 cancer.

25

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

30

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

35

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

40

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

5

Experimental Details

As used herein, the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
μL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
i. v. (intravenous);	Hz (Hertz);
MHz (megahertz);	mol (moles);
mmol (millimoles);	rt (room temperature);
min (minutes);	h (h);
mp (melting point);	TLC (thin layer chromatography);
Tr (retention time);	RP (reverse phase);
MeOH (methanol);	<i>i</i> -PrOH (isopropanol);
TEA (triethylamine);	TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride);	THF (tetrahydrofuran);
DMSO (dimethylsulfoxide);	AcOEt (EtOAc);
DME (1,2-dimethoxyethane);	DCM (CH ₂ Cl ₂);
DCE (dichloroethane);	DMF (<i>N,N</i> -dimethylformamide);
DMPU (<i>N,N</i> -dimethylpropyleneurea);	CDI (1,1-carbonyldiimidazole);
IBCF (isobutyl CHCl ₃ ate);	HOAc (acetic acid);
HOSu (<i>N</i> -hydroxysuccinimide);	HOBT (1-hydroxybenzotriazole);
mCPBA (meta-chloroperbenzoic acid);	
BOC (tert-butyloxycarbonyl);	Fmoc (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimide);	CBZ (benzyloxycarbonyl);
Ac (acetyl);	atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl);	TMS (trimethylsilyl);
TIPS (triisopropylsilyl);	TBS (t-butyldimethylsilyl);

- DMAP (4-dimethylaminopyridine); BSA (bovine serum albumin)
 ATP (adenosine triphosphate); HRP (horseradish peroxidase);
 DMEM (Dulbecco's modified Eagle medium);
 HPLC (high pressure liquid chromatography);
 5 BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
 TBAF (tetra-n-butylammonium fluoride);
 HBTU (O-Benzotriazole-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate);
 HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
 DPPA (diphenylphosphoryl azide);
 10 fHNO₃ (fumed HNO₃);
 EDC (ethylcarbodiimide hydrochloride); and
 EDTA (ethylenediaminetetraacetic acid).
 dppf (1,1'-bis(diphenylphosphino)ferrocene)
- 15 All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.
- 20 For examples 1-15:
- ¹H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, a Bruker AVANCE-400, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe
 25 apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).
- Low-resolution mass spectra (MS) were recorded on a Waters micromass ZQ2000; 2695 Alliance; 2996 Photodiode Array Detector. Preparative
 30 LC/MS purification uses the following condition:
 Waters FractionLynx LC/MS condition
- Autosampler/Fractioncollector: 2767 Inject collector
 - Waste collector: waters fraction collector2
 - HPLC: 2525 pump
 - 35 • Detector: 2996 Photodiode Array Detector
 - MS: ZQ2000
 - Make up pump: waters reagent manager
- Purification protocol
- Loading: 5-100 mg,
 - 40 • 4 gradient methods, Cycle time: 15 min
 - Flow rate: 40 mL/min

- Column: XTerra™MSC₁₈, 30 X 150mm (10 μmm)
- Injection Volume: 1800 μL
- Temperature: rt

Basic condition mobile phase

5 A- (PureH₂O: 3L+ 28% Ammonia solution 11mL)

B - 100% Acetonitrile

Acidic condition mobile phase

A- (PureH₂O :3L+ 100% Formic acid 3mL)

B – (Acetonitrile: 3L + 100% Formic acid 3mL)

10

Make up solvent

20%H₂O + 80%Methanol + 10 mM ammonium acetate

Gradient: 6 gradient methods for purification (Solvent B ratio)

Time	flow	Method1	Method2	Method3	Method4	Method5	Method6
0	1	5	5	5	5	5	5
0.5	40	5	5	5	5	5	5
1	40	5	10	20	35	50	65
10	40	25	25	40	55	75	90
13.5	40	100	100	100	100	100	100
15	40	100	100	100	100	100	100

- 15 All mass spectra were taken under electrospray ionization (ESI), chemical ionization (CI), and electron impact (EI) or by fast atom bombardment (FAB) methods. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution or mass spectrometry (electrospray or AP). Flash column chromatography was performed on silica gel (230-400 mesh, Merck) or using automated silica gel chromatography (Yamazen Fast Flow Liquid Chromatography, UV detection triggering sample collection).
- 20
- 25 Microwave irradiation was performed on a Personal Chemistry Smithsynthesizer or Creator.
- SCX purification: Varian Mega Bond Elut SCX; General procedure: A SCX cartridge was rinsed with MeOH, and then crude mixture was dissolved into a suitable solvent such as MeOH, DCM etc. and loaded on the cartridge.
- 30 And then the cartridge was rinsed with methanol and dichloromethane successively. The product was isolated by elution with a 2M ammonia

solution in methanol (for some cases, mixed with DCM), followed by concentration *in vacuo*.

For examples 16-30:

5 Chromatographic purification was performed using pre-packed Bond Elut silica gel cartridges available commercially from Varian.

NMR

10 ¹H NMR spectra were recorded in DMSO-*d*₆ on a Bruker DPX 400 working at 400 MHz. The internal standard used was either tetramethylsilane or the residual protonated solvent at 2.50 ppm for DMSO-*d*₆.

Mass Directed Autopreparative HPLC

15 Autopreparative HPLC was carried out using a Waters 600 gradient pump, Waters 2767 inject/collector, Waters Reagent Manager, Micromass ZMD mass spectrometer, Gilson Aspec waste collector and Gilson 115 post-fraction UV detector. The column used was typically a Supelco LCABZ++ column with dimension of 20mm internal diameter by 100mm in length. The stationary phase particle size is 5µm. The flow rate was 20ml/min and the runtime was 15 minutes, which comprises a 10-minute gradient followed by
20 a 5 minute column flush and re-equilibration step.

Solvent A: Aqueous solvent = water + 0.1% formic acid.

25 Solvent B: Organic solvent = MeCN: water 95:5 + 0.05% formic acid

Specific gradients used were dependent upon the retention time in the analytical system. For 1.5-2.2 min, 0-30% B, 2.0-2.8 min, 5-30% B, 2.5-3.0 min, 15-55%B, 2.8-4.0 min, 30-80% B and 3.8-5.5 min, 50-90% B.

30 LCMS System

The LCMS system used was as follows:

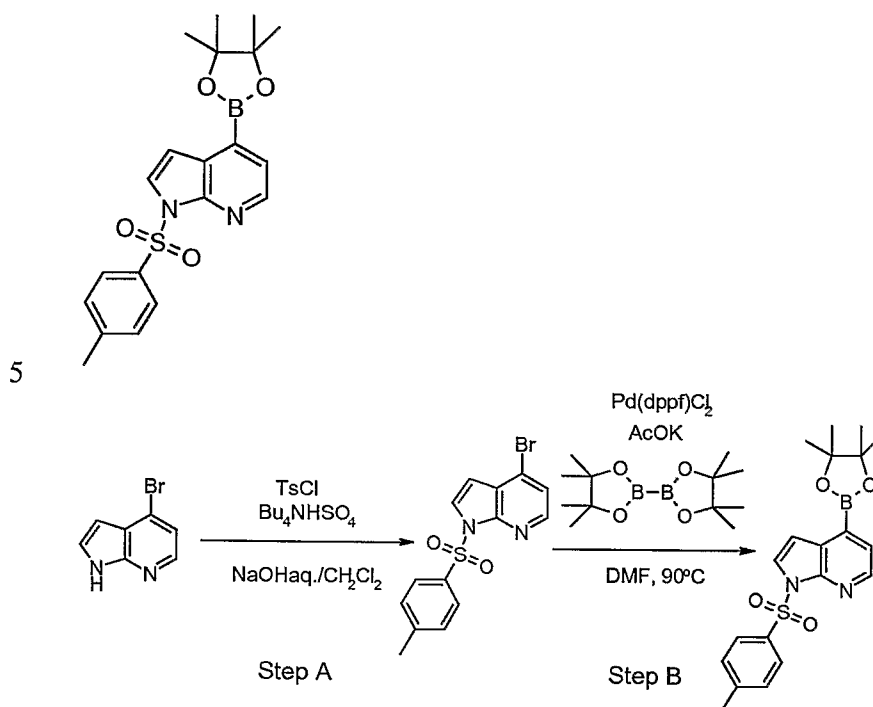
- 35
- Column: 3.3 cm x 4.6 mm ID, 3 µm ABZ+PLUS from Supelco
 - Flow Rate: 3 ml/min
 - Injection Volume: 5 µl
 - Temp: rt
 - UV Detection Range: 215 to 330 nm

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.

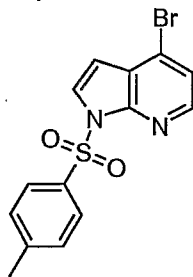
B: 95% Acetonitrile + 0.05% Formic Acid

Gradient: Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

Intermediate 1: 1-[(4-Methylphenyl)sulfonyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine



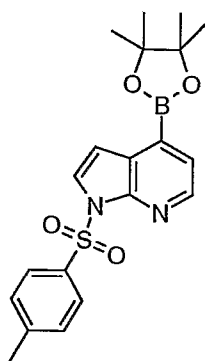
Step A: 4-Bromo-1-[(4-methylphenyl)sulfonyl]-1H-pyrrolo[2,3-b]pyridine



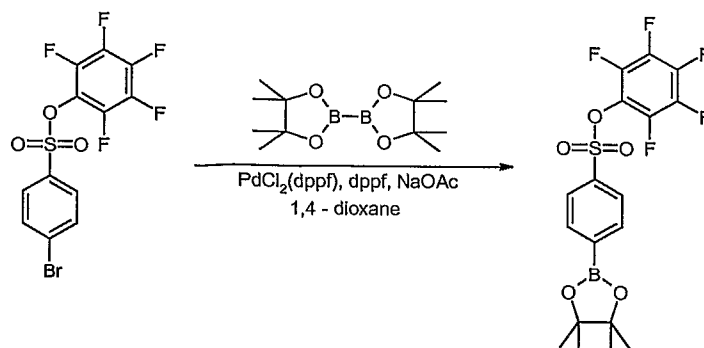
- 10 Aqueous NaOH (6N, 5 mL) was added to a solution of 4-bromo-1H-pyrrolo[2,3-b]pyridine (1.6 g, 8.1 mmol), TsCl (3.1 g, 2.0 mmol) and Bu₄NHSO₄ (82.7 mg, 0.3 mmol) in CH₂Cl₂ (40 mL). The reaction mixture was stirred at rt for 30 min. After that, the reaction was diluted with saturated aqueous solution of NH₄Cl, and

- extracted with CH_2Cl_2 (20mL X 3 times). The organic layer was washed by brine, dried over Na_2SO_4 , and then evaporated under reduced pressure. The residue was purified by silica gel chromatography ($\text{EtOAc:Hex} = 1:4$), and the corresponding product was obtained as a white solid (2.0 g, 70 %). ^1H NMR ppm (400MHz, DMSO- d_6) 2.35 (s, 3H), 6.79 (d, 1H, $J = 4.0$ Hz), 7.43 (d, 2H, $J = 8.1$ Hz), 7.61 (d, 1H, $J = 5.3$ Hz), 8.00 (d, 2H, $J = 8.1$ Hz), 8.04 (d, 1H, $J = 4.0$ Hz), 8.25 (d, 1H, $J = 5.1$ Hz). LC/MS: m/z 351 (M-1)-, 353 (M+2)+

- Step B: 1-[(4-Methylphenyl)sulfonyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-*b*]pyridine

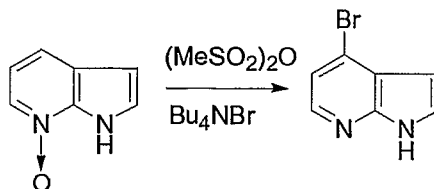


- 4-Bromo-1-[(4-methylphenyl)sulfonyl]-1H-pyrrolo[2,3-*b*]pyridine (1.9 g, 5.4 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.8 g, 10.9 mmol), KOAc (1.6 g, 16.3 mmol) and Pd(dppf)Cl_2 (0.4 g, 0.5 mmol) in DMF (20 mL) was refluxed for 48 h under inert atmosphere. After cooling to rt, 1N aqueous solution of NaOH was added till the aqueous layer was taken to pH 10. The above mixture was washed with CH_2Cl_2 . Then the aqueous layer was carefully acidified to pH 4 with 1N HCl aqueous solution. Extracted with CH_2Cl_2 (20mL X 3 times), and the organic layer was concentrated under reduced pressure, and the desired boronic ester was obtained as a brown solid in moderate yield (1.7 g, 77 %). ^1H NMR (400MHz, DMSO- d_6) ppm 1.32 (s, 12H), 2.33 (s, 3H), 6.95 (d, 1H, $J = 4.0$ Hz), 7.40 (d, 2H, $J = 8.1$ Hz), 7.47 (d, 1H, $J = 4.5$ Hz), 7.93-7.98 (m, 3H), 8.38 (d, 1H, $J = 4.5$ Hz). LC/MS: m/z 397 (M-1)-, 399 (M+1)+
- Intermediate 2: Pentafluorophenyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonate (90 mg 0.2 mmol)**



(Note: Prior to the reaction the 1,4-dioxane solvent was nitrogen purged / deoxygenated)

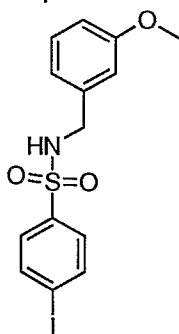
- To a solution of 4-Bromo-PFP-sulphonate ester (25 g, 62 mmol) in 1,4-dioxane (875 mL) under an atmosphere of nitrogen were added pinacolato diboron (17.27g, 68.2 mmol, 1.1 eq), $\text{PdCl}_2(\text{dppf})$ catalyst (1.52 g, 1.86 mmol, 0.03 eq), dppf (1.03 g, 1.86 mmol, 0.03 eq) and NaOAc (30.52 g, 372 mmol, 6 eq) to form a orange/red suspension. The reaction mixture was covered in tin foil as to exclude light, before being stirred at reflux (105 °C) for 16 h. After this period hplc analysis showed the reaction had gone to completion, with no start material ($r_t = 1.99$ min) observed. The reaction mixture was cooled to rt and the dark inorganic material removed by filtration, washing the material with DCM (3 x 200 mL). The organic filtrate was concentrated *in vacuo* to yield a black solid residue (approx. 45 g). The material was suspended/washed in water (600 mL) and vigorously stirred to help break up the solid material. (NOTE: The majority of the material was soluble in water). The aqueous phase was then extracted with Et_2O (3 x 300 ml). (NOTE: During the extractions brine was introduced to help distinguish a phase boundary. Insoluble material also had a tendency to fluctuate between the phases).
- The combined Et_2O extracts were combined, washed with brine (300 mL), dried on MgSO_4 and filtered. The organic filtrate was concentrated *in vacuo* to yield a red residual oil. The residue was boiled in hexane (3 x 300 mL) and filtered through fluted filter paper while still hot (the product is soluble in hot hexane). The combined hexane filtrates were concentrated *in vacuo*, and the residue re-crystallised using a minimum volume of hot methyl-*tert*-butyl-ether (MTBE) (approx. 150 mL). Upon allowing the ether solution to cool, 'scratching' was performed to help induce crystallisation. The solid material was collected by filtration and dried under vacuum to yield the title compound as a pale brown / cream solid (3.58 g). The methyl-*tert*-butyl-ether filtrate was concentrated *in vacuo* and re-crystallised again using a minimum volume of hot MTBE to yield a further 0.52 g of the title compound. The re-crystallisation procedure was repeated twice more, this time using 50:50 Hexane : Et_2O . These procedures accumulated in 6.15 g of the title compound being isolated. Combined mass total = 10. 21g, 37 % yield

Intermediate 3: 4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine

- 5 1*H*-Pyrrolo[2,3-*b*]pyridine oxide (50 g, 373 mmol) and tetramethylammonium bromide (86 g, 559 mmol) were stirred into DMF (500 mL) at room temperature and then cooled to 0 °C. Methanesulphonic anhydride was then run into the stirred mixture over about half an hour. Stirring was continued for a further 4 h during which time the reaction warmed to rt. This mixture was then poured onto water (1
- 10 L) with stirring and carefully neutralised (pH = 7) by the addition of sodium hydroxide solution. A further amount of water was added (1.5 L) followed by ice so that the temperature of the stirred suspension was reduced to about 10 °C. The solid was then removed by filtration and washed with ice/water. The solid was dried in the air and then stirred in cold DCM (80 mL) for half an hour before being
- 15 collected by filtration, washed with a further small amount of DCM and then dried. This gave the product, 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine as a tan solid (34.55 g, 175.3 mmol, 47%), mp 173-176 °C, R_F 0.45 (EtOAc). HPLC indicated 94-95% purity.

20 **Example 1: *N*-[3-(Methoxy)phenyl]methyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide**

Step A: 4-Iodo-*N*-[3-(methoxy)phenyl]methylbenzenesulfonamide



- 25 4-Iodobenzenesulfonyl chloride (0.5 mmol) was added to a solution of 1-[3-(methoxy)phenyl]methanamine (0.5 mmol) in pyridine (5 mL). Then, the mixture was stirred at rt for 1 h. The solvent was removed *in vacuo* to obtain 4-iodo-*N*-[3-(methoxy)phenyl]methylbenzenesulfonamide which was utilized in the next step without characterization.

30

Step B: *N*-[3-(Methyloxy)phenyl]methyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

Sulfonamide obtained above (0.1 mmol) and 1-[(4-methylphenyl)sulfonyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (0.15 mmol) were dissolved in DME (2 mL), and aqueous Na₂CO₃ (2M, 0.2 mL). The resulting solution and Pd(PPh₃)₄ (20 mol%) were added to a Microwave vial (2-5 mL). After capping, the mixture was heated with SmithSynthesizer at 120 °C for 60 min. The mixture was filtered and washed with MeOH. To the filtrate, aqueous solution of 6N NaOH (0.1 mL) was added. After stirring at 50 °C for 1h, the reaction mixture was eluted with saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂. The organic phase was purified by SCX cartridge via capture-and-release. Concentration *in vacuo* and purification by mass directed LC/MS gave the title compound as a pale yellow crystal without the calculation of the yield. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 3.66 (s, 3H), 4.06 (d, 2H, *J* = 5.8 Hz), 6.63 (dd, 1H, *J* = 2.0, 3.3 Hz), 6.74-6.80 (m, 2H), 6.83 (d, 1H, *J* = 7.6 Hz), 7.18 (t, 1H, *J* = 7.8 Hz), 7.24 (d, 1H, *J* = 5.1 Hz), 7.61 (dd, 1H, *J* = 2.8, 3.3 Hz), 7.91-7.94 (m, 4H), 8.26-8.31 (m, 1H, *J* = 6.3 Hz), 8.33 (d, 1H, *J* = 5.1 Hz), 11.90 (brs, 1H). LC/MS: *m/z* 392 (M-1)⁻, 394 (M+1)⁺

Example 2: *N*-[2-(4-Morpholinyl)-1-phenylethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 1** was used, with [2-(4-morpholinyl)-1-phenylethyl]amine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 2.21-2.31 (m, 4H), 3.34-3.42 (m, 6H), 4.36-4.45 (m, 1H), 6.57 (dd, 1H, *J* = 2.0, 3.5 Hz), 7.10-7.27 (m, 5H), 7.53-7.61 (m, 1H), 7.61 (dd, 1H, *J* = 2.8, 3.5 Hz), 7.81 (d, 2H, *J* = 8.8 Hz), 7.84 (d, 2H, *J* = 8.8 Hz), 8.19 (d, 1H, *J* = 7.6 Hz), 8.32 (d, 1H, *J* = 4.8 Hz), 11.90 (brs, 1H). LC/MS: *m/z* 461 (M-1)⁻, 463 (M+1)⁺

Example 3: *N*-[2-(Dimethylamino)-2-phenylethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 1** was used, with (2-amino-1-phenylethyl)dimethylamine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 1.99 (s, 6H), 3.09-3.14 (m, 1H), 3.47 (t, 1H, *J* = 7.1 Hz), 6.65 (dd, 1H, *J* = 1.8, 3.5 Hz), 7.15-7.18 (m, 2H), 7.25-7.27 (m, 1H), 7.27-7.34 (m, 2H), 7.61 (dd, 2H, *J* = 2.8, 3.5 Hz), 7.62-7.70 (m, 1H), 7.93 (d, 2H, *J* = 8.8 Hz), 7.96 (d, 2H, *J* = 8.8 Hz), 8.33 (d, 1H, *J* = 5.1 Hz), 11.90 (brs, 1H). LC/MS: *m/z* 419 (M-1)⁻, 421 (M+1)⁺

Example 4: *N*-Phenyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

5 A similar procedure as **Example 1** was used, with aniline substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 6.60 (dd, 1H, *J* = 1.8, 3.3 Hz), 7.03 (ddd, 1H, *J* = 1.0, 6.3, 7.3 Hz), 7.14 (dd, 1H, *J* = 1.3, 8.8 Hz), 7.22-7.27 (m, 3H), 7.58 (dd, 1H, *J* = 2.5, 3.3 Hz), 7.92 (d, 1H, *J* = 8.8 Hz), 7.95 (d, 1H, *J* = 8.8 Hz), 8.29 (d, 1H, *J* = 4.8 Hz), 10.42 (brs, 1H), 11.89 (brs, 1H). LC/MS: 348 (M-1)⁻, 350 (M+1)⁺

10

Example 5: *N*-[2-(Dimethylamino)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

15 A similar procedure as **Example 1** was used, with *N,N*-dimethyl-1,2-ethanediamine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 2.06 (s, 6H), 2.27 (t, 2H, *J* = 7.1 Hz), 2.89 (t, 2H, *J* = 7.1 Hz), 6.64 (dd, 1H, *J* = 1.0, 3.5 Hz), 7.26 (d, 1H, *J* = 4.8 Hz), 7.61 (dd, 1H, *J* = 2.3, 3.5 Hz), 7.65 (brs, 1H), 7.96 (d, 2H, *J* = 8.6 Hz), 7.99 (d, 2H, *J* = 8.6 Hz), 8.32 (d, 1H, *J* = 4.8 Hz), 11.91 (brs, 1H). LC/MS: *m/z* 343 (M-1)⁻, 345 (M+1)⁺

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Example 6: *N*-[3-(Dimethylamino)propyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

25 A similar procedure as **Example 1** was used, with *N,N*-dimethyl-1,3-propanediamine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 1.48-1.55 (m, 2H), 2.04 (s, 6H), 2.17 (t, 2H, *J* = 7.1 Hz), 2.84 (t, 2H, *J* = 6.6 Hz), 6.64 (dd, 1H, *J* = 2.0, 3.5 Hz), 7.26 (d, 1H, *J* = 4.8 Hz), 7.61 (dd, 1H, *J* = 2.8, 3.5 Hz), 7.72 (brs, 1H), 7.94 (d, 2H, *J* = 8.6 Hz), 8.00 (d, 2H, *J* = 8.6 Hz), 8.33 (d, 1H, *J* = 4.8 Hz), 11.90 (brs, 1H). LC/MS: 357 (M-1)⁻, 359 (M+1)⁺

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Example 7: *N*-[2-(4-Morpholinyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

35 A similar procedure as **Example 1** was used, with [2-(4-morpholinyl)ethyl]amine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 2.26-2.35 (m, 6H), 2.94 (t, 2H, *J* = 6.6 Hz), 3.47-3.51 (m, 4H), 6.64 (d, 1H, *J* = 3.5 Hz), 7.26 (d, 1H, *J* = 5.1 Hz), 7.61 (d, 1H, *J* = 3.5 Hz), 7.68 (brs, 1H), 7.96 (d, 2H, *J* = 8.8 Hz), 7.99 (d, 2H, *J* = 8.8 Hz), 8.33 (d, 1H, *J* = 5.1 Hz), 11.88 (s, 1H). LC/MS: *m/z* 385 (M-1)⁻, 387 (M+1)⁺

40

Example 8: *N*-(2-Aminoethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 1** was used, with (2-aminoethyl)amine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 2.59 (t, 2H, *J* = 6.6 Hz), 2.81 (t, 2H, *J* = 6.6 Hz), 6.65 (d, 1H, *J* = 3.5 Hz), 7.27 (d, 1H, *J* = 4.8 Hz), 7.60 (d, 1H, *J* = 3.5 Hz), 7.95 (d, 2H, *J* = 8.8 Hz), 8.00 (d, 2H, *J* = 8.8 Hz), 8.33 (d, 1H, *J* = 5.1 Hz), 11.90 (brs, 1H). LC/MS: *m/z* 315 (M-1)⁻, 316 (M+1)⁺

Example 9: *N*-(3-[[2-(Dimethylamino)ethyl]oxy]propyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 1** was used, with {2-[(3-aminopropyl)oxy]ethyl}dimethylamine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 1.59-1.66 (m, 2H), 2.10 (s, 6H), 2.34 (d, 2H, *J* = 5.8 Hz), 2.87 (dd, 2H, *J* = 6.8, 12.6 Hz), 6.65 (dd, 1H, *J* = 2.0, 3.3 Hz), 7.26 (d, 1H, *J* = 4.8 Hz), 7.61 (dd, 1H, *J* = 2.5, 3.3 Hz), 7.75 (d, 1H, *J* = 5.8 Hz), 7.94 (d, 2H, *J* = 8.6 Hz), 8.00 (d, 2H, *J* = 8.6 Hz), 8.33 (d, 1H, *J* = 4.8 Hz), 11.90 (s, 1H). LC/MS: *m/z* 401 (M-1)⁻, 403 (M+1)⁺

Example 10: *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 1** was used, with 4-(2-aminoethyl)benzenesulfonamide substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 2.81 (d, 2H, *J* = 6.8 Hz), 3.08 (d, 2H, *J* = 6.8 Hz), 6.65 (dd, 1H, *J* = 1.0, 3.3 Hz), 7.27 (d, 1H, *J* = 5.1 Hz), 7.29 (brs, 2H), 7.39 (d, 2H, *J* = 8.6 Hz), 7.60 (dd, 1H, *J* = 2.3, 3.3 Hz), 7.73 (d, 2H, *J* = 8.6 Hz), 7.86 (s, 1H), 7.94 (d, 2H, *J* = 8.6 Hz), 7.99 (d, 2H, *J* = 8.6 Hz), 8.33 (d, 1H, *J* = 5.1 Hz), 11.90 (brs, 1H). LC/MS: *m/z* 455 (M-1)⁻, 457 (M+1)⁺

Example 11: *N*-(2-(1*H*-Indol-2-yl)ethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 1** was used, with [2-(1*H*-indol-2-yl)ethyl]amine 2-(1*H*-indol-2-yl)ethanamine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 2.84 (d, 2H, *J* = 7.8 Hz), 3.08 (dd, 2H, *J* = 5.8, 7.8 Hz), 6.64 (dd, 1H, *J* = 1.8, 3.5 Hz), 6.94 (ddd, 1H,

$J = 1.0, 7.1, 7.8$ Hz), 7.04 (ddd, 1H, $J = 1.0, 7.1, 8.1$ Hz), 7.14 (d, 1H, $J = 2.3$ Hz), 7.25 (d, 1H, $J = 4.8$ Hz), 7.31 (d, 1H, $J = 8.1$ Hz), 7.40 (d, 1H, $J = 7.8$ Hz), 7.60 (dd, 1H, $J = 2.8, 3.5$ Hz), 7.87 (t, 1H, $J = 5.8$ Hz), 7.95 (d, 2H, $J = 8.8$ Hz), 7.97 (d, 2H, $J = 8.8$ Hz), 8.32 (d, 1H, $J = 4.8$ Hz), 10.82 (brs, 1H), 11.89 (brs, 1H). LC/MS: m/z 415 (M-1)⁻, 417 (M+1)⁺

Example 12: *N*-[2-(1-Piperazinyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

10 A similar procedure as **Example 1** was used, with [2-(1-piperazinyl)ethyl]amine 2-(1-piperazinyl)ethanamine substituting for {[3-(methyloxy)phenyl]methyl}amine, to prepare the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 2.20-2.27 (m, 4H), 2.28-2.34 (m, 2H), 2.65 (t, 2H, $J = 4.8$ Hz), 2.93 (t, 2H, $J = 6.8$ Hz), 6.64 (dd, 1H, $J = 1.8, 3.3$ Hz), 7.26 (d, 1H, $J = 4.8$ Hz), 7.61 (dd, 1H, $J = 2.8, 3.3$ Hz), 7.64 (brs, 1H), 7.96 (d, 2H, $J = 8.8$ Hz), 7.99 (d, 12H, $J = 8.8$ Hz), 8.33 (d, 1H, $J = 4.8$ Hz), 11.90 (brs, 1H). LC/MS: m/z 384 (M-1)⁻, 386 (M+1)⁺

Example 13: 4-[4-(1-Pyrrolidinylsulfonyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine

20 4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine (20 mg, 0.1mmol) and 1-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl]pyrrolidine (44 mg, 0.13 mmol) were dissolved in DME (1.5 mL) and aqueous Na₂CO₃ (2M, 0.5 mL). The resulting solution and Pd(PPh₃)₄ (10 mol%) were added to a Microwave vial (2-5 mL). After capping, the mixture was heated with Creator at 120 °C for 1 h. The mixture was filtered and washed with MeOH/CH₂Cl₂. The filtrate was purified by SCX cartridge via capture-and-release. Concentration *in vacuo* and purification by mass directed LC/MS gave the title compound without the calculation of the yield. ¹H NMR (400 MHz, DMSO-*d*₆) ppm 1.68-1.73 (m, 4H), 3.19-3.25 (m, 4H), 6.67 (d, 1H, $J = 3.5$ Hz), 7.28 (d, 1H, $J = 5.1$ Hz), 7.62 (d, 1H, $J = 3.5$ Hz), 7.94-8.06 (m, 4H), 8.34 (d, 1H, $J = 5.1$ Hz), 11.92 (s, 1H). LC/MS: m/z 326 (M-1)⁻, 328 (M+1)⁺

Example 14: 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

35 A mixture of 1-[(4-methylphenyl)sulfonyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (40 mg, 0.1 mmol), 4-bromobenzenesulfonamide (28 mg, 0.12 mmol), Pd(PPh₃)₄ (12 mg, 0.01 mmol), 2M aqueous Na₂CO₃ (0.2 mL) and DMF (0.5 mL) was heated at 90 to 100 °C for 16h. After cooling, the reaction mixture was filtered through a filter tube (5.0 μm pore size) and washed with MeOH. 40 6M aqueous NaOH (100 mL) was added to the filtrate and the mixture was stirred at 50 °C for 1 to 2 h. The mixture was acidified with 2M HCl and purified by SCX

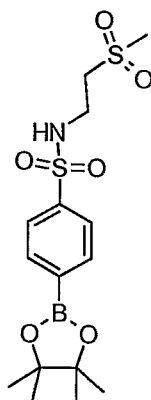
and prep. LC/MS. ^1H NMR (400 MHz, DMSO- d_6) ppm 6.64 (d, 1H, J = 3.5 Hz), 7.26 (d, 1H, J = 4.9 Hz), 7.48 (br, 2H), 7.58-7.63 (m, 1H), 7.94-8.01 (m, 4H), 8.33 (d, 1H, J = 4.9 Hz), 11.91 (br, 1H). LC/MS: m/z 272 (M-1) $^-$, 274 (M+1) $^+$

5 **Example 15: 4-[4-(Methylsulfonyl)phenyl]-1H-pyrrolo[2,3-*b*]pyridine**

A similar procedure as **Example 14** was used, with 4-bromophenyl methyl sulfone substituting for 1-[(4-methylphenyl)sulfonyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-*b*]pyridine, to prepare the title compound. ^1H NMR (400 MHz, DMSO- d_6) ppm 3.30 (s, 3H), 6.65 (d, 1H, J = 3.5 Hz), 7.28 (d, 1H, J = 4.8 Hz), 7.63 (d, 1H, J = 3.5 Hz), 8.02-8.13 (m, 4H), 8.34 (d, 1H, J = 4.8 Hz), 11.94 (br, 1H). LC/MS: m/z 271 (M-1) $^-$, 273 (M+1) $^+$

15 **Example 16: *N*-[2-(Methylsulfonyl)ethyl]-4-(1H-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide**

Step A: *N*-[2-(Methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide



20 Pentafluorophenyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonate (90 mg 0.2 mmol) and [2-(methylsulfonyl)ethyl]amine (24.6 mg) were treated with triethylamine (100 μL) and heated at 150 $^\circ\text{C}$ in a microwave for 10 min to afford *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide which was utilized in the next step without characterization.

25 Step B: *N*-[2-(Methylsulfonyl)ethyl]-4-(1H-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

To a suspension of *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (0.1 mmol) in 5:1 dioxan:water (0.5 mL) was added sodium carbonate (17mg), [1,1'-Bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (4 mg, 5 mol %)

30 and 4-bromo-1H-pyrrolo[2,3-*b*]pyridine (19.5 mg). The reaction mixture was

heated at 150 °C in a microwave for 10 min. The reaction mixture was applied to C18 SPE cartridges and eluted with acetonitrile (3 mL). Concentration *in vacuo* and purification by mass directed HPLC gave the title compound. LC/MS: Tr = 2.56 min, m/z 380 (M+H)+

5

Example 17: *N*-[(1,1-Dioxidotetrahydro-3-thienyl)methyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

10 A similar procedure as **Example 16** was used, with *N*-[(1,1-dioxidotetrahydro-3-thienyl)methyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.63 min, m/z 406 (M+H)+

15 **Example 18: *N*-(1,1-Dioxidotetrahydro-3-thienyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide**

20 A similar procedure as **Example 16** was used, with *N*-(1,1-dioxidotetrahydro-3-thienyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.61 min, m/z 392 (M+H)+

25 **Example 19: *N*-(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide**

30 A similar procedure as **Example 16** was used, with *N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.6 min, m/z 406 (M+H)+

35 **Example 20: *N*-{3-[(Methylsulfonyl)amino]propyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide**

40 A similar procedure as **Example 16** was used, with *N*-{3-[(methylsulfonyl)amino]propyl}-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.6 min, m/z 409 (M+H)+

Example 21: *N*-[2-(Aminosulfonyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 16** was used, with *N*-[2-(aminosulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.5 min, m/z 381 (M+H)+

Example 22: 4-Methyl-*N*-[2-({[4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)phenyl]sulfonyl}amino)ethyl]benzenesulfonamide

A similar procedure as **Example 16** was used, with 4-methyl-*N*-[2-({[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl}amino)ethyl]benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 3.09 min, m/z 471 (M+H)+

Example 23: *N*-[3-(Aminosulfonyl)propyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 16** was used, with *N*-[3-(aminosulfonyl)propyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.5 min, m/z 395 (M+H)+

Example 24: *N*-[2-[(Methylamino)sulfonyl]ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 16** was used, with *N*-[2-[(methylamino)sulfonyl]ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.62 min, m/z 395 (M+H)+

Example 25: *N*-[2-[(Dimethylamino)sulfonyl]ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

40

A similar procedure as **Example 16** was used, with *N*-{2-[(dimethylamino)sulfonyl]ethyl}-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.77 min, m/z 409 (M+H)+

Example 26: *N*-{2-[(4-Methyl-1-piperazinyl)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 16** was used, with *N*-{2-[(4-methyl-1-piperazinyl)sulfonyl]ethyl}-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.13 min, m/z 464 (M+H)+

Example 27: *N*-{2-[(Phenylamino)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 16** was used, with *N*-{2-[(phenylamino)sulfonyl]ethyl}-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 3.03 min, m/z 457 (M+H)+

Example 28: *N*-{2-[(Ethylamino)sulfonyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide

A similar procedure as **Example 16** was used, with *N*-{2-[(ethylamino)sulfonyl]ethyl}-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.73 min, m/z 409 (M+H)+

Example 29: 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzenesulfonamide

A similar procedure as **Example 16** was used, with *N*-(tetrahydro-2*H*-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. LC/MS: Tr = 2.69 min, m/z 358 (M+H)+

Example 30: 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)-*N*-[(3*S*)-tetrahydro-3-furanyl]benzenesulfonamide

- 5 A similar procedure as **Example 16** was used, with *N*-[(3*S*)-tetrahydro-3-furanyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide substituting for *N*-[2-(methylsulfonyl)ethyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, to prepare the title compound. It is believed that the final compound obtained is of the same chirality as the intermediate used. LC/MS: Tr =
 10 2.65 min, m/z 344 (M+H)⁺

Example 31 - Capsule Composition

- 15 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 I, below.

Table I

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
<i>N</i> -{[3-(Methyloxy)phenyl]methyl}-4-(1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-4-yl)benzenesulfonamide	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

20 Example 32 - Injectable Parenteral Composition

- 25 An injectable form for administering the present invention is produced by stirring 1.5% by weight of *N*-[2-(4-Morpholinyl)-1-phenylethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide in 10% by volume propylene glycol in water.

Example 33 - Tablet Composition

- 30 The sucrose, calcium sulfate dihydrate and an Akt inhibitor as shown in Table II 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 II

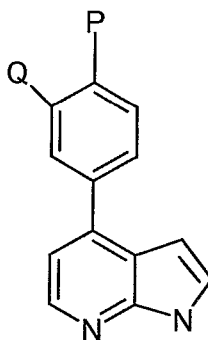
<u>INGREDIENTS</u>	<u>AMOUNTS</u>
<i>N</i> -[2-(Dimethylamino)-2-phenylethyl]-4-(1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-4-yl)benzenesulfonamide	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

- 5 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.

10

What is claimed is:

1. A compound of Formula (I):



wherein:

either:

P is hydrogen and Q is $-Z-R^1$;

or:

Q is hydrogen and P is $-Z-R^1$;

and in either case:

Z is selected from the group consisting of $-SO_2-$, $-CONR^{20}-$, $-N(R^{25})CO-$, $-N(R^{25})CONR^{20}-$, $-SO_2NR^{20}-$, where R^{20} is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkoxy and halo C_1 - C_6 alkyl, and R^{25} is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkoxy and halo C_1 - C_6 alkyl; and

R^1 is C_1 - C_6 alkyl or is a group $-NR^2R^3$, wherein R^2 and R^3 , together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring, or R^2 is hydrogen and R^3 is selected from:

hydrogen;

tetrahydrofuranyl;

tetrahydropyranyl;

$-Y-NR^4R^5$, where Y is selected from $-(CH_2)_p-$, $-(CH_2)_pCHR^6-$, $-CHR^6(CH_2)_p-$, $-C_1$ - C_6 alkoxy C_1 - C_6 alkyl- and $-(CH_2)_pSO_2-$, where p is 1, 2 or 3,

R^6 is phenyl, and R^4 and R^5 are independently selected from hydrogen and C_1 - C_6 alkyl, or R^4 and R^5 taken together with the nitrogen to which they are attached form a morpholinyl or a piperazinyl group, the morpholinyl or piperazinyl group being optionally substituted by C_1 - C_6 alkyl; or R^4 is hydrogen and R^5 is selected from C_1 - C_6 alkylsulphonyl, phenyl and phenylsulfonyl, the phenyl and the phenyl moiety in the phenylsulfonyl group being optionally substituted by C_1 - C_6 alkyl; and

$-(CH_2)_m-X$ wherein m is 0, 1 or 2 and X is selected from phenyl, phenyl substituted with from one to three substituents selected from $-C_1$ - C_6 alkyl,

-C₁₋₆alkoxy and sulfamoyl, thiocyclopentane-1,1-dioxide, thiocyclohexane-1,1-dioxide and indolyl.

2. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (I), as described in claim 1.
3. A compound as claimed in claim 1, wherein R¹ is methyl, a pyrrolidinyl ring or -NH₂.
4. A compound as claimed in claim 1, wherein R₁ is a group -NR₂R₃, wherein R₂ is hydrogen and R₃ is:
 - tetrahydrofuranyl; or
 - tetrahydropyranyl; or
 - a group -(CH₂)_m-X wherein m is 0 or 1 or 2 and X is phenyl (optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy or sulfamoyl), thiocyclopentane-1,1-dioxide, thiocyclohexane-1,1-dioxide or indolyl; or
 - a group -(CH₂)_pNR₄R₅, wherein p is 1, 2 or 3, R₄ and R₅ are independently hydrogen or C₁₋₆alkyl, or R₄ and R₅ form a morpholinyl or a piperazinyl group, the morpholinyl or a piperazinyl group being optionally substituted by C₁₋₆alkyl; or R₄ is hydrogen and R₅ is C₁₋₆alkylsulphonyl or phenylsulfonyl, the phenyl moiety in the phenylsulfonyl group being optionally substituted by C₁₋₆alkyl; or
 - a group -(CH₂)_pCHR₆NR₄R₅ or -CHR₆(CH₂)_pNR₄R₅, p is 1 or 2, R₆ is phenyl, R₄ and R₅ are independently hydrogen or C₁₋₆alkyl, or R₄ and R₅ form a morpholinyl or a piperazinyl group, the morpholinyl or a piperazinyl group being optionally substituted by C₁₋₆alkyl; or
 - a group -C₁₋₆alkoxyC₁₋₆alkyl-NR₄R₅, wherein R₄ and R₅ are independently hydrogen or C₁₋₆alkyl; or
 - a group -(CH₂)_pSO₂NR₄R₅, wherein p is 2 or 3, R₄ and R₅ are independently hydrogen or C₁₋₆alkyl, or R₄ is hydrogen and R₅ is phenyl, the phenyl being optionally substituted by C₁₋₆alkyl, or R₄ and R₅ form a piperazinyl group, the piperazinyl group being optionally substituted by C₁₋₆alkyl.
5. A compound as claimed in claim 3, wherein R₁ is a group -NR₂R₃, wherein R₂ is hydrogen and R₃ is:
 - tetrahydrofuranyl; or
 - tetrahydropyranyl; or
 - a group -(CH₂)_m-X wherein m is 0 or 1 or 2 and X is phenyl (optionally substituted by methoxy or sulfamoyl), thiocyclopentane-1,1-dioxide, thiocyclohexane-1,1-dioxide or indolyl; or

- a group $-(CH_2)_pNR_4R_5$, wherein p is 1, 2 or 3, R_4 and R_5 are independently hydrogen, methyl or ethyl, or R_4 and R_5 form a morpholinyl or a piperazinyl group, the morpholinyl or a piperazinyl group being optionally substituted by methyl or ethyl; or R_4 is hydrogen and R_5 is C_{1-6} alkylsulphonyl or phenylsulfonyl, the phenyl moiety in the phenylsulfonyl group being optionally substituted by methyl or ethyl; or
- a group $-(CH_2)_pCHR_6NR_4R_5$ or $-CHR_6(CH_2)_pNR_4R_5$, p is 1 or 2, R_6 is phenyl, R_4 and R_5 are independently hydrogen or methyl, or R_4 and R_5 form a morpholinyl group, optionally substituted by methyl or ethyl; or
- a group $-(CH_2)_qO(CH_2)_qNR_4R_5$, wherein q is independently 2 or 3 and R_4 and R_5 are independently hydrogen, methyl or ethyl; or
- a group $-(CH_2)_pSO_2NR_4R_5$, wherein p is 2 or 3, R_4 and R_5 are independently hydrogen, methyl or ethyl, or R_4 is hydrogen and R_5 is phenyl, the phenyl being optionally substituted by methyl or ethyl, or R_4 and R_5 form a piperazinyl group, the piperazinyl group being optionally substituted by methyl or ethyl.

6. A compound of claim 1 selected from:
- N -{[3-(methyloxy)phenyl]methyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[2-(4-morpholinyl)-1-phenylethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[2-(dimethylamino)-2-phenylethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -phenyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[2-(dimethylamino)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[3-(dimethylamino)propyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[2-(4-morpholinyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -(2-aminoethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -(3-{[2-(dimethylamino)ethyl]oxy}propyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -{2-[4-(aminosulfonyl)phenyl]ethyl}-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[2-(1*H*-indol-2-yl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[2-(1-piperazinyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- 4-[4-(1-Pyrrolidinylsulfonyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine;
- 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- 4-[4-(Methylsulfonyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine;
- N -[2-(methylsulfonyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
- N -[(1,1-dioxidotetrahydro-3-thienyl)methyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;

- N*-(1,1-dioxidotetrahydro-3-thienyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
N-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 5 *N*-[3-[(methylsulfonyl)amino]propyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
N-[2-(aminosulfonyl)ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 4-methyl-*N*-[2-([4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)phenyl]sulfonyl)amino]ethyl]benzenesulfonamide;
 10 *N*-[3-(aminosulfonyl)propyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
N-[2-[(methylamino)sulfonyl]ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
N-[2-[(dimethylamino)sulfonyl]ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 15 *N*-[2-[(4-methyl-1-piperazinyl)sulfonyl]ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
N-[2-[(phenylamino)sulfonyl]ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
N-[2-[(ethylamino)sulfonyl]ethyl]-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzenesulfonamide;
 20 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzenesulfonamide;
 and
 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-*N*-[(3*S*)-tetrahydro-3-furanyl]benzenesulfonamide.
- 25 7. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of claim 6.
8. A method of manufacturing a compound as claimed in any of claims 1-5, the method comprising:

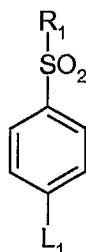
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- a) reacting a compound of formula (II):



(II)

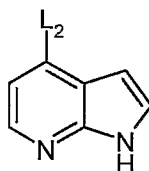
wherein R' and R'' are independently hydrogen or C₁₋₆alkyl, or R' and R'' form a 5 or 6 membered ring optionally substituted by 1 to 4 C₁₋₆alkyl groups; with a compound of formula (III):



(III)

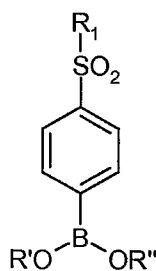
wherein R₁ is as defined for formula (I) in claim 1 and L₁ is a leaving group; or

b) reacting a compound of formula (IV):



(IV)

wherein L₂ is a leaving group, with a compound of formula (V):



(V)

wherein R₁ is as defined for formula (I) in claim 1, R' and R'' are independently hydrogen or C₁₋₆alkyl or R' and R'' form a 5 or 6 membered ring optionally substituted by 1 to 4 C₁₋₆alkyl groups;

and thereafter optionally for process (a) or process (b):

- removing any protecting groups;
- forming a pharmaceutically acceptable salt;

- converting a compound of formula (I) to another compound of formula (I).

9. A pharmaceutical composition comprising a compound claimed in any of claims 1-5 and a pharmaceutically acceptable carrier.

5

10. A compound as claimed in any of claims 1-5 or a pharmaceutical composition as claimed in claim 8 for use in therapy.

10 11. A method of treating or lessening the severity of a disease or condition selected from cancer and arthritis in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound as claimed in any of claims 1 -5.

15 12. A method of treating cancer in a mammal in need thereof, which comprises: administering to such mammal a therapeutically effective amount of
a) a compound as claimed in any of claims 1-5; and
b) at least one anti-neoplastic agent.

20 13. The method as claimed in claim 10 or claim 11, wherein the cancer is selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

25 14. A method of inhibiting Akt activity in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound as claimed in any of claims 1-5.

30 15. The method as claimed in any of claims 10-13, wherein the mammal is a human.

16. Use of a compound as claimed in any of claims 1-5 in the manufacture of a medicament for use in treating or lessening the severity of a disease or condition selected from cancer and arthritis.

35 17. Use of
a) a compound as claimed in any of claims 1-5; and
b) at least one anti-neoplastic agent
in the manufacture of a medicament for use in treating cancer in a mammal in need thereof.

40

18. Use as claimed in claim 15 or 16, wherein the cancer is selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

5

19. Use of a compound as claimed in any of claims 1-5 in the manufacture of a medicament for use in inhibiting Akt activity in a mammal in need thereof.

SEQUENCE LISTING

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