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(54) Title: INHIBITORS OF AKT ACTIVITY

(57) Abstract: Invented are novel 1 H-imidazo[4,5-c]pyridin-2-yl compounds, the use of such compounds as inhibitors of protein kinase B activity and in the treatment of cancer and arthritis.



WO 2007/058879 A2

## INHIBITORS OF Akt ACTIVITY

### FIELD OF THE INVENTION

5 This invention relates to novel 1H-imidazo[4,5-c]pyridin-2-yl compounds, the use of such compounds as inhibitors of protein kinase B (hereinafter PKB/Akt, PKB or Akt) activity and in the treatment of cancer and arthritis.

### BACKGROUND OF THE INVENTION

10 The present invention relates to 1H-imidazo[4,5-c]pyridin-2-yl containing compounds that are inhibitors of the activity of one or more of the 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  
15 arthritis (Liu et al. Current Opin. Pharmacology 3:317-22 (2003)).

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  
20 the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x<sub>L</sub>, 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  
25 proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science*, 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*  
30 385:544-548 (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  
35 phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P<sub>3</sub>), 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 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, 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 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 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 PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Nati. 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 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 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 $\alpha$ , Akt2/PKB $\beta$ , and Akt3/PKB $\gamma$  respectively. The isoforms are homologous, 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 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)).

Phosphorylation of Akt1/PKB $\alpha$  occurs on two regulatory sites, Thr<sup>308</sup> in the catalytic domain activation loop and on Ser<sup>473</sup> 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 $\beta$  and Akt3/PKB $\gamma$ . 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)-P<sub>3</sub>, 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  
10 .chemotherapeutic agents.

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

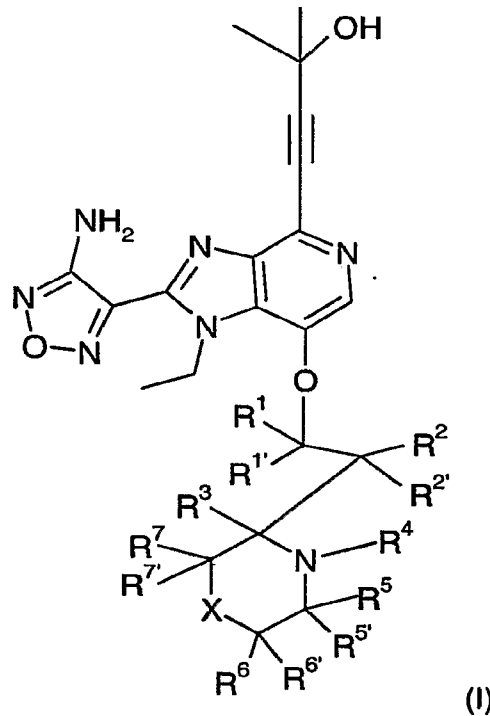
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the  
15 methods of the invention.

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

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



5

wherein:

X is absent or selected from the group consisting of: O, S and  $CR^{20}R^{21}$ ,  
 where  $R^{20}R^{21}$  are independently selected from: hydrogen, fluorine,  
 cyclopropyl, cyclobutyl, cyclopentyl, and  $-C_1-C_4$ alkyl;

10

$R^1R^{1'}$  are independently selected from: hydrogen, fluorine, cyclopropyl,  
 cyclobutyl, cyclopentyl, and  $-C_1-C_4$ alkyl;

15

$R^2R^{2'}$  are independently selected from: hydrogen, fluorine, cyclopropyl,  
 cyclobutyl, cyclopentyl, and  $-C_1-C_4$ alkyl;

$R^3$  is selected from the group consisting of: hydrogen and  $-C_1-C_4$ alkyl; and  
 when X is absent or  $CR^{20}R^{21}$ ,  $R^1$  can additionally be fluorine;

20

$R^4$  is selected from the group consisting of: hydrogen, cyclopropyl,  
 cyclobutyl, cyclopentyl, and  $-C_1-C_4$ alkyl;

R<sup>5</sup>R<sup>5'</sup> are independently selected from: hydrogen, fluorine, cyclopropyl, cyclobutyl, cyclopentyl, and -C<sub>1</sub>-C<sub>4</sub>alkyl;

5 R<sup>6</sup>R<sup>6'</sup> are independently selected from: hydrogen, fluorine, cyclopropyl, cyclobutyl, cyclopentyl, and -C<sub>1</sub>-C<sub>4</sub>alkyl;

R<sup>7</sup>R<sup>7'</sup> are independently selected from: hydrogen, fluorine, cyclopropyl, cyclobutyl, cyclopentyl, and -C<sub>1</sub>-C<sub>4</sub>alkyl; and

10

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

15 This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

20 This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

20

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

25 In a further aspect of the invention there is provided novel processes useful in preparing the presently invented Akt/PKB inhibiting compounds.

30 Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

30

Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

#### DETAILED DESCRIPTION OF THE INVENTION

35

International Application No. PCT/US2004/024340, having an International filing date of July 28, 2004; International Publication Number WO 2005/011700 and an International Publication date of February 10, 2005, the schemes, processes

and assays of which are hereby incorporated by reference, discloses and claims 1H-imidazo[4,5-c]pyridin-2-yl containing compounds, along with pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof, as being useful as inhibitors of serine/threonine kinase, Akt (also known as protein kinase B), particularly in the treatment of cancer and arthritis. International Application No. PCT/US2004/024340 does not specifically disclose any of the compounds within the scope of this application.

It has now been found that the compounds of Formula (I) exhibit advantages over what is considered to be the most structurally related compounds disclosed in International Application No. PCT/US2004/024340.

For example, the compounds of Examples 1, 2 and 3 of the present invention generally exhibit enhanced activity and enhanced selectivity for the inhibition of tumor cell growth over inhibition of normal cell growth when compared to what is considered to be the most structurally related compounds disclosed in International Application No. PCT/US2004/024340. This enhanced activity and enhanced selectivity is expected to result in a wider therapeutic window. Additionally, the compounds disclosed in International Application No. PCT/US2004/024340 generally exhibit poor solubility in water. One aspect of this poor solubility is that it adversely affects the ability of these compounds to be formulated into pharmaceutical dosage forms suitable for intravenous (hereinafter IV) administration. In addition to generally having enhanced activity and enhanced selectivity for the inhibition of tumor cell growth over inhibition of normal cell growth, the compounds of Examples 1, 2, and 3 of the present invention exhibit solubility that is considered suitable for formulation into dosage forms for IV administration. Intravenous administration is an advantageous method for administering the compounds of the present invention.

While the compounds of International Application No. PCT/US2004/024340 are useful as inhibitors of serine/threonine kinase, AKT (also known as protein kinase B), the compounds of Formula (I), particularly the compounds of Examples 1, 2 and 3 generally exhibit advantageous properties, such as appropriate solubility, activity, selectivity, clearance and exposure, which overall render them advantageous over what is considered to be the most structurally related compounds disclosed in International Application No. PCT/US2004/024340.

This invention relates to compounds of Formula (I) as described above.

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.

Included among the presently invented compounds of Formula (I) are:

4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-pyrrolidinyl]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol;

4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-piperidinyl]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol; and

4-(2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-{{2-(3-thiomorpholinyl)ethyl}oxy})-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol;

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

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 substituents cyclopropyl, cyclobutyl, cyclopentyl and -C<sub>1</sub>-C<sub>4</sub>alkyl, are optionally substituted with from 1 fluorine atom to where the substituent is perfluorinated. Suitably, the substituent is optionally substituted with from 1 to 8 fluorine atoms. By the term "perfluorinated" as used herein is meant a substituent where all of the hydrogen atoms have been replaced by fluorine atoms.

By the term "-C<sub>1</sub>-C<sub>4</sub>alkyl" as used herein, is meant a linear or branched, saturated or unsaturated hydrocarbon chain, containing from 1 to 4 carbon atoms. Examples of -C<sub>1</sub>-C<sub>4</sub>alkyl as used herein include: -CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>-CF<sub>3</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>, -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>3</sub>, -CH=CH<sub>2</sub>, and -C≡C-CH<sub>3</sub>.

Unless otherwise stated, the compounds disclosed herein also include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

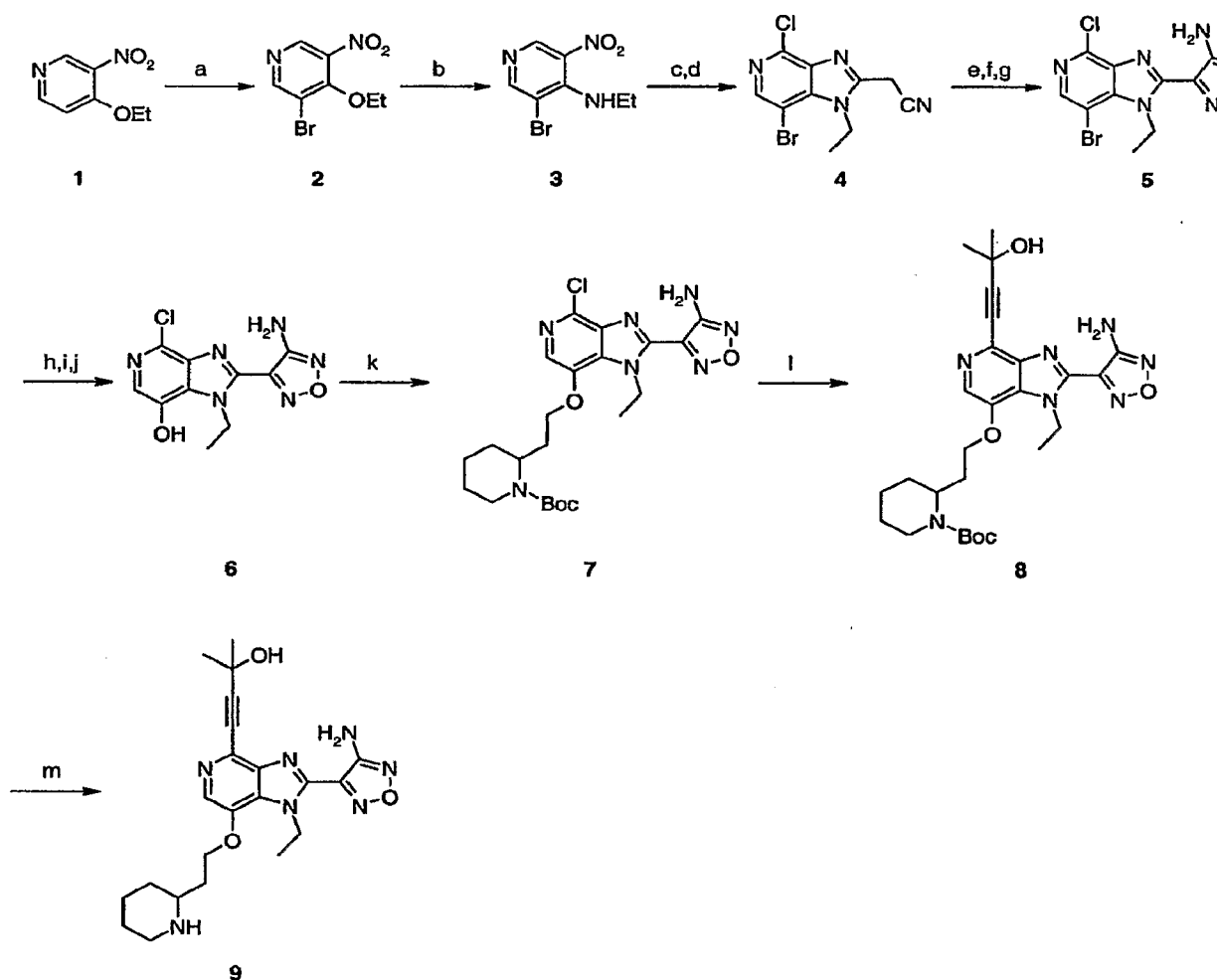
By the term "treating" and derivatives thereof as used herein, is meant prophylactic and therapeutic therapy.

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 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.

The novel compounds of Formula I are prepared as shown in Scheme 1 below, or by analogous methods. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

10

Scheme 1

(a)  $\text{Br}_2$ , NaOAc; (b)  $\text{EtNH}_2$ ; (c)  $\text{SnCl}_2$ , HCl; (d) ethyl cyanoacetate,  $190^\circ\text{C}$ ; (e)  $\text{NaNO}_2$ , HCl; (f)  $\text{NH}_2\text{OH}$ ; (g)  $\text{Et}_3\text{N}$ , dioxane; (h)  $n\text{-BuLi}$ , THF; (i)  $\text{B}(\text{OMe})_3$ ; (j)  $\text{H}_2\text{O}_2$ , NaOH; (k) 1,1-dimethylethyl 2-(2-hydroxyethyl)-1-piperidinecarboxylate, DEAD,

polymer bound  $\text{PPh}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; (l)  $\text{Pd}(\text{PPh}_3)_4$ ,  $i\text{Pr}_2\text{NH}$ , dioxane, 100 °C; (m) TFA,  $\text{CH}_2\text{Cl}_2$ .

Compounds of Formula (I) can be prepared in a manner analogous to those shown  
5 in Scheme 1. Bromination of 3-nitro-4-ethoxy pyridine (1-Scheme 1) using bromine  
buffered in sodium acetate gives 3-bromo-4-(ethoxy)-5-nitropyridine (2-Scheme  
1). Other alternative methods exist and are known to those skilled in the art for  
carrying out this transformation. A compilation of these methods can be found in  
10 standard organic synthesis texts such as Larock, "Comprehensive Organic  
Transformations," VCH, N.Y.(1989). The ethoxy group is then displaced by a  
primary amine such as ethyl amine in a polar solvent such as ethanol to give  
compounds such as 3-Scheme 1. In the case liquid amines, the reaction can be  
carried out in the absence of solvent. The reduction of the nitro group with  
15 concomitant introduction of the chloro group is achieved using tin (II) chloride  
according to the method described by Kelley et al. J. Med. Chem. 1995, 38(20),  
4131-34. The corresponding 5-bromo-2-chloro diaminopyridine is condensed with  
an appropriate acid or ester such as ethyl cyanoacetate. Continued heating affects  
a cyclodehydration reaction to give imidazopyridines such as 4-Scheme 1.  
Reaction with  $\text{NaNO}_2$  in concentrated HCl following by reaction with hydroxylamine  
20 gives a bis-oxime that cyclodehydrates in the presence of an appropriate base such  
as triethylamine to give an aminofurazan such as 5-Scheme 1. The hydroxyl group  
is introduced by generating an aryl anion by halogen-metal exchange using a  
suitable base such as n-butyl lithium, reacting the anion with an appropriate boron  
electrophile such as trimethyl borate and oxidizing the resulting aryl boronate with  
25 an appropriate oxidizing agent such as hydrogen peroxide in aqueous base to give  
imidazopyridinols such as 6-Scheme 1. Other bases such as Grignard reagents  
can also be used to affect the halogen metal exchange. Etherification of the  
imidazopyridinol is carried out with an appropriate alcohol such as 1,1-dimethylethyl  
(3-hydroxypropyl)carbamate using the methods described by Mitsunobu, Synthesis  
30 1981, 1 to give ethers such as 7-Scheme 1. Treatment of an appropriate aryl  
halide such as 7-Scheme 1 with an appropriate catalyst such as  
tetrakis(triphenylphosphine) palladium and a terminal alkyne in the presence of a  
suitable base such as di-isopropylamine in an appropriate solvent such as dioxane  
gives the corresponding aryl alkyne such as 8-Scheme 1. Removal of the  
35 protecting groups is achieved using a protic or Lewis acid such as trifluoroacetic

acid in a polar solvent such as methylene chloride giving compounds of Formula (I) such as 9-Scheme 1.

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, 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 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), 6<sup>th</sup> 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 triazines; 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 (anti-neoplastic agent) 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.

5 Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G<sub>2</sub>/M phases of the cell cycle. It is believed that the diterpenoids stabilize the  $\beta$ -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,  
10 but are not limited to, paclitaxel and its analog docetaxel.

Paclitaxel, 5 $\beta$ ,20-epoxy-1,2 $\alpha$ ,4,7 $\beta$ ,10 $\beta$ ,13 $\alpha$ -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  
15 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  
20 (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.

25 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.,  
30 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  
35 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 $\beta$ -20-epoxy-1,2 $\alpha$ ,4,7 $\beta$ ,10 $\beta$ ,13 $\alpha$ -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.

Vincristine, vincalukoblastine, 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 gastrointestinal mucositis effects occur.

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

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing

adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

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

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

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino,  
15 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 triazines such as dacarbazine.

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

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

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

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

5 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  
10 carmustine.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea,  
15 vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

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

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

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

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy- $\alpha$ -L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-  
35 5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for

the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

5           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  
10 limiting side effects of bleomycin.

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

          Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G<sub>2</sub>  
15 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

          Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single  
20 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.  
25

          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  
30 combination with other chemotherapy agents in the treatment of acute leukemia in children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide can induce both leucopenia and thrombocytopenia.

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

fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

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

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

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

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

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride ( $\beta$ -isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S

boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

Methotrexate, N-[4[[[(2,4-diamino-6-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 treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

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

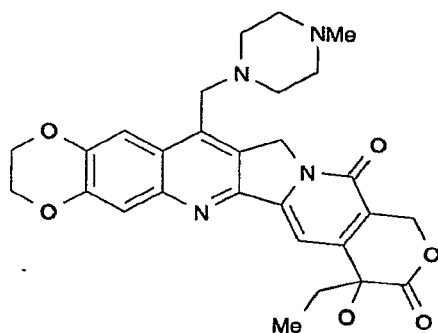
Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irinotecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for

second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.

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



known by the chemical name "7-(4-methylpiperazino-methylene)-10,11-  
 10 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;  
 15 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  
 20 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  
 25 carcinoma containing estrogen receptors; progestrins such as megestrol acetate  
 useful in the treatment of hormone dependent breast cancer and endometrial  
 carcinoma; estrogens, androgens, and anti-androgens such as flutamide,  
 nilutamide, bicalutamide, cyproterone acetate and 5 $\alpha$ -reductases such as  
 finasteride and dutasteride, useful in the treatment of prostatic carcinoma and  
 30 benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene,

raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

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

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

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor -I (IGFI) receptor, macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther.

Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, London.

5 Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases for use 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  
10 tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

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

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular  
20 Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta). Ikb kinase family (IKKa, IKKb), PKB family kinases, akt kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T.,  
25 Taya, S., Kaibuchi, K., (1999), Journal of Biochemistry. 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), Biochemical Pharmacology, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., and Harris, A.L. (1995), Cancer Treatment and Research. 78: 3-27, Lackey, K. et al Bioorganic and Medicinal Chemistry Letters, (10), 2000, 223-226; U.S. Patent No.  
30 6,268,391; and Martinez-Iacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

Inhibitors of Phosphatidylinositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku may also be 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)  
35 3301-3308; Jackson, S.P. (1997), International Journal of Biochemistry and Cell Biology. 29 (7):935-8; and Zhong, H. et al, Cancer res, (2000) 60(6), 1541-1545.

Also of interest in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myo-inositol 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  
5 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras  
10 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.

As mentioned above, antibody antagonists to receptor kinase ligand binding  
15 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  
20 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.*  
25 (2000) 60, 5117-5124).

Non-receptor kinase angiogenesis inhibitors may also be useful 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  
30 signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Accordingly, non-receptor tyrosine kinase inhibitors may be used in combination with the compounds 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  
35 ( $\alpha_v\beta_3$ ) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed compounds. (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. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of signaling pathways using a small molecule inhibitor. Discussion of the immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT et al. (2000), *Cancer Res.* 60: 3569-3576; and Chen Y, Hu D, Eling DJ, Robbins J, and Kipps TJ. (1998), *Cancer Res.* 58: 1965-1971.

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are discussed in Water JS et al. (2000), *J. Clin. Oncol.* 18: 1812-1823; and Kitada S et al. (1994), *Antisense Res. Dev.* 4: 71-79.

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

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

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

          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  
10           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.

15

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  
20           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-  
25           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  
30           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  
35           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.

5 His-tagged 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  
10 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-  
15 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 MgCl<sub>2</sub>, 4uM ATP, 8uM peptide, 0.04 uCi [g-<sup>33</sup>P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test  
20 compound in 100% DMSO. The reaction was stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg<sup>2+</sup> and Ca<sup>2+</sup>, 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  
25 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  $100 \cdot (U1 - C2) / (C1 - C2)$  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  
30 curve described by:  $y = ((Vmax \cdot x) / (K + x))$  where Vmax is the upper asymptote and K is the IC50.

Cloning of full-length human (FL) AKT1:

35 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: SEQ. ID NO: 2  
5' TATATAGGATCCATGAGCGACGTGGC 3' and the 3' primer: SEQ. ID NO: 3  
AAATTTCTCGAGTCAGGCCGTGCTGCTGG 3'. The 5' primer included a BamHI site  
5 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 Cysteine<sup>25</sup> was converted to the wild-type AKT1  
sequence (CGC) coding for an Arginine<sup>25</sup> by site-directed mutagenesis using the  
QuikChange<sup>®</sup> Site Directed Mutagenesis Kit (Stratagene). The AKT1 mutagenic  
10 primer: SEQ. ID NO: 4 5' ACCTGGCGGCCACGCTACTTCCTCC and selection  
primer: SEQ. ID NO: 5 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  
15 (Invitrogen).

#### Expression of FL human AKT1:

Expression was done using the BAC-to-BAC Baculovirus Expression System from  
20 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.

#### 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  
30 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  
35 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.

5 The Q-HP column was washed with 3 column volume (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, 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  
10 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.

15

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

#### Full-Length AKT Enzyme Assay

20

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  
25 the catalytic domains of AKT 1, 2, or 3. 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-ARKRERAYSGHHA-amide). Substrate phosphorylation was detected by the following procedure.

30

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 MgCl<sub>2</sub>, 4uM ATP, 8uM peptide, 0.04 uCi [g-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  
35 (Dulbecco's PBS without Mg<sup>2+</sup> and Ca<sup>2+</sup>, 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  $100 \cdot (U1 - C2) / (C1 - C2)$  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:  $y = (V_{max} \cdot x) / (K + x)$  where Vmax is the upper asymptote and K is the IC50.

The compound of Example 1 demonstrated an IC50 (uM) activity of: 0.002 uM, FL AKT1; and 0.008 uM, FL AKT2 in the above full-length AKT enzyme assay.

Activity against tumor cell lines and a normal cell line and the solubilities of the compounds of Examples 1 to 3 of this invention were compared to what is considered to be the most structurally related compounds prepared in International Application No. PCT/US2004/024340. Specifically, the compound of Example 140 in International Application No. PCT/US2004/024340 (compound 4-(1-ethyl-7-[[3-(4-morpholinyl)propyl]oxy]-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine trifluoroacetate, hereinafter Compound R), the compound of Example 151 in International Application No. PCT/US2004/024340 (compound 1-[[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridin-7-yl]oxy]-3-(4-morpholinyl)-2-propanol trifluoroacetate, hereinafter Compound S), the compound of Example 152 in International Application No. PCT/US2004/024340 (compound 4-(1-ethyl-7-[[2-(4-morpholinyl)ethyl]oxy]-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine trifluoroacetate, hereinafter Compound T), the compound of Example 17 in International Application No. PCT/US2004/024340 (compound 4-[1-ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridine-2-yl]-fuzazan-3-ylamine trifluoroacetate, hereinafter Compound U), the compound of Example 127 in International Application No. PCT/US2004/024340 (compound: 4-{1-ethyl-4-phenyl-7-[(3-piperidinylmethyl)oxy]-1H-imidazo-[4,5-c]pyridin-2-yl}-1,2,5-oxadiazol-3-amine trifluoroacetate, hereinafter Compound V), the compound of Example 215 in International Application No. PCT/US2004/024340 (compound 4-[7-[(4-aminobutyl)oxy]-2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-4yl]-2-methyl-3-butyn-2-ol trifluoroacetate, hereinafter Compound W), the compound of Example 222 in International Application No. PCT/US2004/024340 (compound 4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-aminopropyl)oxy]-1-ethyl-1H-imidazo[4,5-c]pyridin-4yl}-2-methyl-3-butyn-2-ol trifluoroacetate, hereinafter

Compound X), the compound of Example 223 in International Application No. PCT/US2004/024340 (compound: 4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[(4-piperidinylmethyl)oxy]-1H-imidazo[4,5-c]pyridin-4-yl}-2-methyl-3-butyn-2-ol trifluoroacetate, hereinafter Compound Y) and the compound of Example 265 in  
5 International Application No. PCT/US2004/024340 (compound: 4-(2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[[3-({2-[4-(methyloxy)phenyl]ethyl}amino)propyl]oxy]-1H-imidazo[4,5-c]pyridin-4-yl)-2-methyl-3-butyn-2-ol, hereinafter Compound Z).

Compounds R, S, T, U, V, W, X, Y and Z can be prepared as described in International Application No. PCT/US2004/024340.

10

Cellular Assays: Methylene Blue Growth Inhibition assay

Tumor cell lines used in this assay were BT474 (human breast carcinoma) and LNCaP (lymph node metastasis of prostate cancer). HFF (normal human foreskin  
15 fibroblast) was also included. All cell lines were cultured in RPMI 1640 media (Invitrogen Corporation 22400-071) containing 10% Fetal Bovine Serum (FBS) at 37°C in a humidified 5% CO<sub>2</sub> incubator. Cells were harvested using trypsin/EDTA, counted using a hemacytometer and plated in 96-well tissue culture plates (Costar 35-3075), 100 uL per well, at the following densities: BT474 15,000 cells/well,  
20 LNCaP 5,000 cells/well and HFF 5,000 cells/well. 10mM stocks of compounds in DMSO were serially diluted in DMSO through nine 3-fold dilutions in 96-well plates (Costar Corning 3363), and stored at -80C. The next day, compound dilutions were thawed and 4 uL of each transferred to 662 uL RPMI 1640 + 100 ug/mL  
25 gentamicin, resulting in twice the final required test concentrations. 100 uL of compounds diluted in RPMI 1640 were added to all cell lines. The final concentration of DMSO in all wells, including controls, was 0.3%. Cells were incubated at 37C, 5% CO<sub>2</sub> for 3 days. Medium was removed by aspiration. Cell biomass was estimated by staining cells with 80 uL methylene blue (Sigma M9140, 0.5% in 50:50 ethanol:water), and incubating at room temperature for 1 hour. Stain  
30 was aspirated and the plates rinsed by immersion in water, then air-dried. Stain was released from cells by adding 100 uL of solubilizing solution (1% N-lauroyl sarcosine, sodium salt, Sigma L5125, in PBS) and incubating at room temperature for at least 30 minutes. Plates were shaken and the optical density at 620 nm was measured on a microplate reader. Percent inhibition of cell growth was calculated  
35 relative to vehicle-treated control wells. Concentration of compound that inhibits 50% of cell growth (IC<sub>50</sub>) was interpolated using non-linear regression (Levenberg-

Marquadt) and the equation,  $y=V_{max}*(1-(x^n/K^n+x^n))+Y_2$ . [Ref: Mager, M. E. (1972) Data Analysis in Biochemistry and Biophysics. New York: Academic Press]

Examples	Methylene Blue Growth Inhibition Assay, IC50 (uM)			Solubility in 50 mM phosphate buffer at pH 7.4 (uM)
	BT474 (human breast carcinoma)	LNCaP (lymph node metastasis of prostate cancer)	HFF (normal human foreskin fibroblast)	
Compound R	17.71	1.42	19.9	0
Compound S	>30	7.77	>30	Not tested
Compound T	>30	>30	18.9	0
Compound U	4.51		6.47	200
Compound V	1.870	1.640	0.57	9
Compound W	8.211	0.836	22.07	210
Compound X	0.241	0.258	18.147	173
Compound Y	2.593	0.217	>30	159
Compound Z	0.266	0.048	5.507	37
Example 1	0.176	0.052	12.63	222
Example 2	0.255	0.065	14.23	200
Example 3	0.026	0.007	3.59	7

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 parenteral.

15 The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers

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

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

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of 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 and/or parenteral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound.

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.

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.

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.

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.

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

5 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.

10 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.

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.

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

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

20

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

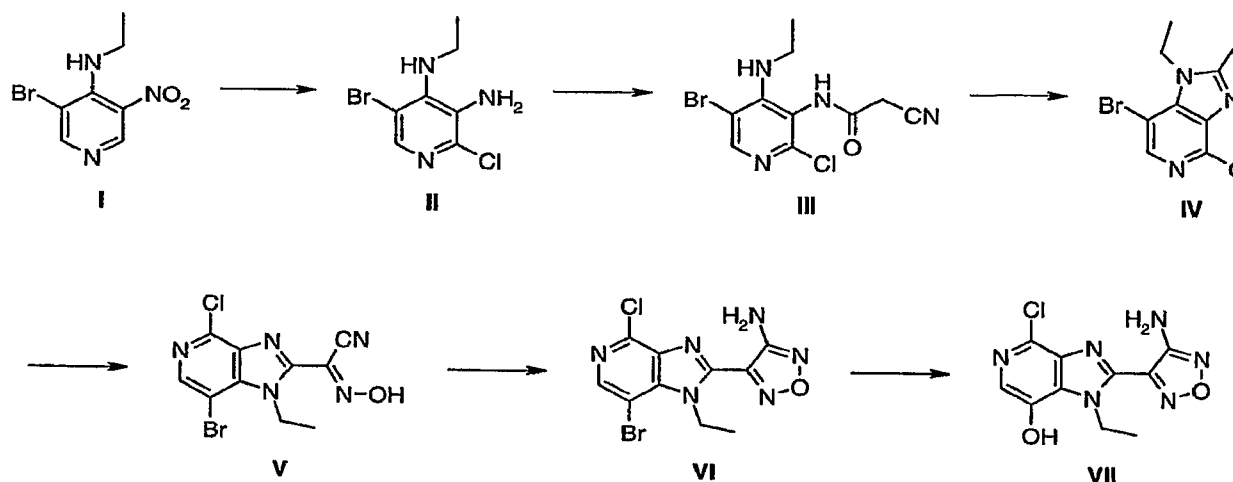
25

#### Experimental Details

The compounds of Examples 1 and 2 are readily made according to Scheme 1 or by analogous methods.

30

#### Intermediate VII



Preparation of 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ol

5

a) 5-Bromo-2-chloro-N<sup>4</sup>-ethyl-pyridine-3,4-diamine (II)

3-Bromo-5-nitropyridin-4-yl)amine (I, 700 g, 2.86 mol) was dissolved in conc HCl (7L) and heated to 85 °C. Tin (II) chloride (1626 g, 8.58 mol) was added in portions. The reaction was heated at reflux for 1 h and then allowed to cool to ambient temperature overnight. The resulting yellow precipitate was collected by filtration, suspended in ice water (5L) and the mixture was adjusted to pH 12 with 12N NaOH. The resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 4 L) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure to give 550 g (77% yield) of the desired compound (II). This was used in the next step without further purification. MS (ES<sup>+</sup>) m/z 250(M+H)<sup>+</sup>.

b) N-[5-Bromo-2-chloro-4-(ethylamino)-3-pyridinyl]-2-cyanoacetamide (III)

To a solution of 5-bromo-2-chloro-N<sup>4</sup>-ethyl-pyridine-3,4-diamine (II, 550 g, 2.21 mol) in CH<sub>2</sub>Cl<sub>2</sub> (5.5 L) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (634.5 g, 3.31 mol), cyanoacetic acid (282 g, 3.31 mol) and N-methylmorpholine (897 g, 8.84 mol). A significant exotherm (~20 °C) was observed upon the addition of the 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and cyanoacetic acid. After stirring at ambient temperature for 2 h, the solvent was removed under reduced pressure. The

resulting residue was extracted with warm EtOAc (40 °C, 20 L) and water (40 °C, 8 L). The aqueous layer was washed with addition EtOAc (10 L) and the combined organic extracts were washed with water (10 L). The organic extract was concentrated under reduced pressure to a slurry and filtered. The solid was washed with EtOAc and dried to give 534 g (76% yield) of the desired compound (III) as a white crystalline solid. This was used in the next step without further purification. MS (ES+) m/z 317(M+H)<sup>+</sup>.

c) (7-Bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-hydroxyimino-acetonitrile (V)

A solution of N-[5-bromo-2-chloro-4-(ethylamino)-3-pyridinyl]-2-cyanoacetamide III, (458 g, 1.45 mol) in glacial acetic acid (4.6 L) was heated to 100 °C. After 3 h, LC/MS analysis indicated that the conversion to (7-bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)acetonitrile (IV) was completed. After allowing to cool to ambient temperature, the reaction was charged with sodium nitrate (230 g, 3.34 mol) in portions. Vigorous gas evolution and foaming was observed together with a ~10 °C exotherm. After stirring at ambient temperature for 16 h, the solid was collected by filtration and dried to a constant weight to give 545 g of the desired product (V) as a light yellow solid. This was used in the next step without further purification. MS (ES+) m/z 328(M+H)<sup>+</sup>.

d) 4-(7-Bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine (VI)

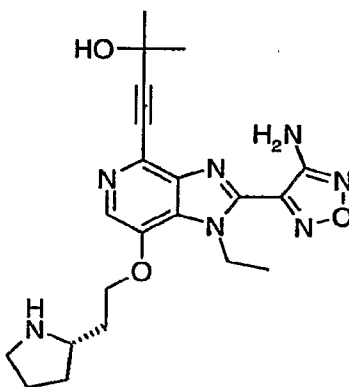
To a mixture of (7-bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-hydroxyimino-acetonitrile (V, 545 g, 1.45 mol) in dioxane (5 L) was added triethylamine (1 L) and hydroxylamine (143 g, 55% in water). The reaction was heated at reflux for 6 h. After cooling the reaction to ambient temperature, the mixture was filtered and the filtrate concentrated under reduced pressure to give a brown solid. The solid was suspended in methanol (1 L) and the suspension was stirred at 65 °C for 0.5 h. The solid was collected by filtration and dried to give 321 g (70% yield) of the desired compound (VI). This was used in the next step without further purification. MS (ES+) m/z 343(M+H)<sup>+</sup>.

e) 2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ol (VII)

A suspension of 4-(7-bromo-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine (VI, 50 g, 0.14 mol) in THF (1 L) was cooled in a dry-ice/acetone bath until the internal temperature was below -75 °C. Isopropyl magnesium chloride (225 mL, 2M in ether, 0.45 mol) was added slowly at a rate to keep the reaction temperature below -70 °C. After an additional 10 min., trimethyl borate (54 mL, 0.48 mol) was added and the reaction was maintained in the dry-ice acetone bath for 1 h. The bath was removed and the reaction was allowed to reach ambient temperature. After 18 h., the resultant yellow suspension was cooled to 0 °C. A solution of 30% hydrogen peroxide (250 mL) and 3N NaOH (100 mL) was added at a rate to keep the reaction temperature below 40 °C. The ice bath was then removed and the reaction was stirred vigorously at ambient temperature for 2 h. The bulk of the organic solvent was removed under reduced pressure and the aqueous layer was acidified to pH 3 with 1N HCl. After stirring the resulting suspension for 30 min., ethyl acetate (200 mL) was added. After stirring for another 1 h, the solid was collected by filtration. The filter cake was washed sequentially with water, ethyl acetate, toluene and ethyl acetate. The solid was dried to a constant weight to give 35.9 g (88% yield) of the desired compound (VII) as a pale yellow solid. This was used without further purification. MS (ES+) m/z 281.3 (M+H)<sup>+</sup>.

20

### Example 1



25

Preparation of 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-((2-[(2S)-2-pyrrolidinyl]ethyl)oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol, bis-trifluoroacetic acid salt

5 a) 1,1-Dimethylethyl (2S)-2-(2-hydroxyethyl)-1-pyrrolidinecarboxylate

To a stirred solution of ((2S)-1-[[1,1-dimethylethyl]oxy]carbonyl)-2-pyrrolidinyl)acetic acid (1.00 g, 4.36 mmol) in THF (30 mL) at 0 °C was added borane-tetrahydrofuran complex (1.0 M solution in THF, 21.8 mL, 21.8 mmol) via syringe over 2 min. After 8 h at 0 °C, a mixture of methanol and acetic acid (9:1,  
10 15 mL) was added with caution. The reaction was warmed to ambient temperature and concentrated in vacuo. The residue was dissolved in ethyl acetate (75 mL) and washed sequentially with 1 N HCl (25 mL), saturated NaHCO<sub>3</sub> (25 mL), and brine (25 mL). The solution was dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure to give 0.90 g of the crude alcohol that was used  
15 in the next step without further purification.

b) 1,1-Dimethylethyl (2S)-2-(2-bromoethyl)-1-pyrrolidinecarboxylate

To a stirred solution of the compound of Example 1(a) (0.90 g, 4.18 mmol) and carbon tetrabromide (1.66 g, 5.03 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0 °C was  
20 added solid triphenylphosphine (1.37 g, 5.22 mmol). After 1.5 h at room temperature, the solvent was removed under reduced pressure and the product isolated by flash chromatography on silica gel to give 0.23 g (19% yield) of the desired compound.

25 c) 1,1-Dimethylethyl (2S)-2-(2-[[2-(4-amino-1,2,5-oxadiazol-3-yl)-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]oxy]ethyl)-1-pyrrolidinecarboxylate

A mixture of the compound of Example 1(b) (0.23 g, 0.83 mmol), the compound of intermediate VII (0.23 g, 0.83 mmol), and cesium carbonate (0.67 g, 2.07 mmol) in DMF (9 mL) was stirred under nitrogen at 35 °C for 16 h. After  
30 allowing the reaction to cool to ambient temperature, the mixture was diluted with ethyl acetate (50 mL) washed with water (3x15 mL) and brine (20 mL). The solution was dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure to give the desired product (>400 mg) that was used in the next step without further purification. MS (ES+) m/z 478.2 (M+H)<sup>+</sup>.

35

d) 1,1-Dimethylethyl (2S)-2-(2-([2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methyl-1-butyn-1-yl)-1H-imidazo[4,5-c]pyridin-7-yl]oxy)ethyl)-1-pyrrolidinecarboxylate

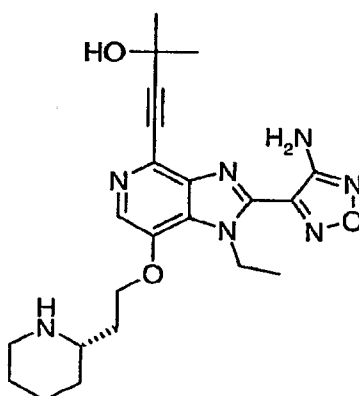
A mixture of the compound of Example 1(c) (0.39 mg, 0.83 mmol), 2-methyl-3-butyn-2-ol (0.20 mL, 2.07 mmol), triethylamine (0.69 mL, 4.95 mmol), DBU (0.25 mL, 1.65 mmol), zinc dust (0.05 g, 0.83 mmol), NaI (0.12 g, 0.83 mmol), and  $(\text{Ph}_3\text{P})_4\text{Pd}$  (0.05 g, 0.04 mmol) was heated at 80 °C under nitrogen in a sealed tube for 2.5 h. The reaction was cooled to ambient temperature, diluted with water (90 mL) and extracted with ethyl acetate (2x100 mL). The combined organic extracts were sequentially washed with water (50 mL) and brine (50 mL), dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography (3-5% MeOH/ $\text{CH}_2\text{Cl}_2$ , silica gel) gave 0.24 g (56% yield) of the desired compound as a pale yellow foam. MS (ES+) m/z 526.4 (M+H)<sup>+</sup>.

e) 4-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-pyrrolidinyl]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol, bis-trifluoroacetate salt

A solution of the compound of Example 1(d) (0.24 g, 0.46 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at ambient temperature was treated with trifluoroacetic acid (1 mL). After 2 h, the solvent was removed under reduced pressure. Preparative HPLC (YMC-Pack ODS-A column, 30 mm i.d. x 75 mm, 20 mL/min, gradient, A: water-0.1% trifluoroacetic acid, B: acetonitrile-0.1% trifluoroacetic acid, 10-90% acetonitrile during 12 min, UV detection at 254 nm) gave 0.24 g (80% yield) of the title compound as a white solid. MS (ES+) m/z 426.2 (M+H)<sup>+</sup>.

25

### Example 2



Preparation of 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-piperidinyl]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol, dihydrochloride

5

a) 1,1-Dimethylethyl (2S)-2-(2-bromoethyl)-1-piperidinecarboxylate

To a solution of 1,1-dimethylethyl (2S)-2-(2-hydroxyethyl)-1-piperidinecarboxylate (0.47 g, 2.04 mmol) and carbon tetrabromide (1.01 g, 3.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) at 0 °C was added drop wise a solution of  
10 triphenylphosphine (0.59 g, 2.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL). The reaction was allowed to warm to ambient temperature. After 18 h, the solvent was removed under reduced pressure. Flash chromatography (0-20% EtOAc/hexanes, silica gel) gave 0.35 g (59% yield) of the desired product as a colorless oil. MS (ES+) m/z 236 (M+H-<sup>t</sup>Bu)<sup>+</sup>.

15

b) 1,1-Dimethylethyl (2S)-2-(2-{{2-(4-amino-1,2,5-oxadiazol-3-yl)-4-chloro-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl}oxy}ethyl)-1-piperidinecarboxylate

A mixture of the compound of intermediate VII (0.31 g, 1.10 mmol), cesium carbonate (0.90 g, 2.75 mmol) and the compound of Example 6(a) (0.35 g, 1.21  
20 mmol) in DMF (5 mL) with was stirred at 40 °C for 3 h. The mixture was then diluted with water and extracted with ethyl acetate. The organic extracts were washed with water, brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was triturated with 10% ethyl acetate in hexanes. The resulting solid was collected by filtration and dried to give 0.42 g  
25 (78% yield) of the desired compound as a beige solid. MS (ES+) m/z 492 (M+H)<sup>+</sup>.

c) 1,1-Dimethylethyl (2S)-2-(2-{{2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methyl-1-butyn-1-yl)-1H-imidazo[4,5-c]pyridin-7-yl}oxy}ethyl)-1-piperidinecarboxylate

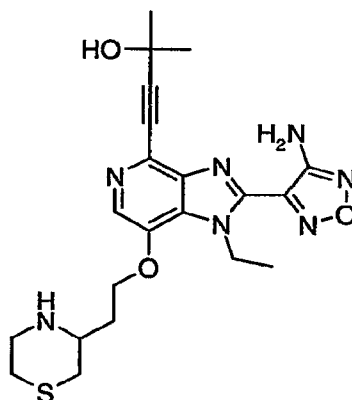
30 A thick-walled pressure vessel was charged with the compound of Example 2(b) (0.42 g, 0.86 mmol), Zn dust (0.02 g, 0.30 mmol), NaI (0.04 g, 0.27 mmol), DBU (0.20 mL, 1.32 mmol), TEA (0.15 mL, 1.07 mmol), 2-methyl-3-butyn-2-ol (0.20 mL, 2.07 mmol) and (Ph<sub>3</sub>P)<sub>4</sub>Pd (0.04 g, 0.03 mmol) in DMSO (5 mL). After purging with nitrogen for 10 min., the reaction vessel was sealed and heated at 80 °C for  
35 2.5 h. The reaction mixture was diluted with water and extracted with ethyl acetate.

The organic extracts were washed with water, brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was triturated with 50% ethyl acetate in hexanes. The resulting solid was collected by filtration and dried to give 0.21 g of the desired compound as a light yellow solid. The  
 5 filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (0-10% MeOH/CHCl<sub>3</sub>, silica gel) to give an additional 0.26 g of the desired compound as light yellow solid. MS (ES+) m/z 540 (M+H)<sup>+</sup>.

d) 4-[2-(4-Amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-piperidiny]ethyl}oxy)-  
 10 1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol, dihydrochloride

To the compound of Example 2(c) (0.21 g, 0.38 mmol) in methanol (5mL) was added 4N HCl in 1,4-dioxane (3.5 mL, 14.0 mmol). After 3 h at ambient temperature, the solvent was removed under reduced pressure. The residue was  
 15 triturated with dichloromethane and the solid was collected by filtration to give 0.17 g of the title compound as light yellow solid. MS (ES+) m/z 440 (M+H)<sup>+</sup>.

### Example 3



20

### Preparation of 4-(2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-(3-thiomorpholinyl)ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl)-2-methyl-3-butyn-2-ol

a) 1,1-Dimethylethyl 3-[2-(ethoxy)-2-oxoethyl]-4-thiomorpholinecarboxylate  
 25 To stirred solution of ethyl-4-bromocrotonate (85% in CH<sub>2</sub>Cl<sub>2</sub>, 11.6 g, 51.0 mmol) at 0°C was added in one portion a mixture of 2-aminoethanethiol (6.9 g, 60.7 mmol) and triethylamine (20 ml) in chloroform (100 mL). The solution was heated

to reflux for 3 h. After allowing the reaction to cool to room temperature, di-tert-butyl dicarbonate (17.5 g, 80 mmol) was added and the resulting solution stirred for 4h. The mixture was partitioned between 1N HCl and chloroform. The organic extract was washed with water, brine and dried over sodium sulfate. The solvent  
5 was removed under reduced pressure and the residue was purified by flash chromatography (0 to 25% ethyl acetate/hexanes, silica gel) to afford 10.5 g of the desired material. MS (ES+) m/z 290 (M+H)<sup>+</sup>.

b) (4-((1,1-Dimethylethyl)oxy)carbonyl)-3-thiomorpholinyl)acetic acid

10 A solution of the compound of Example 3(a) (10.5 g, 36.3 mmol) in methanol (200 mL) and 6N NaOH (25 mL) was stirred at room temperature for 2 h. Water (175 mL) was added and bulk of the organic solvent was removed under reduced pressure. The aqueous solution was washed with ether (100 mL),  
15 acidified with 6N HCl (30 mL) and extracted with ethyl acetate. The combined organic extracts were washed with water, brine and dried over sodium sulfate. The solvent was removed under reduced pressure to give 8.85 g of the desired compound. MS (ES+) m/z 262 (M+H)<sup>+</sup>.

c) 1,1-Dimethylethyl 3-(2-hydroxyethyl)-4-thiomorpholinecarboxylate

20 Borane (1M in THF, 100 mL, 100 mmol) was added over a period of 30 min to a solution of the compound of Example 3(b) (8.6 g, 33 mmol) in THF (100 mL) at 0 °C. The cooling bath was removed and stirring was continued for 2h. The solvent was removed under reduced pressure and the residue was azeotroped two times with methanol. The residue was dissolved in ethyl acetate and washed with  
25 1N HCl, H<sub>2</sub>O, brine and dried over sodium sulfate. The solvent was removed under reduced pressure to give 8.19 g of the desired compound. MS (ES+) m/z 248.3 (M+H)<sup>+</sup>.

d) 1,1-Dimethylethyl 3-(2-([2-(4-amino-1,2,5-oxadiazol-3-yl)-4-chloro-1-ethyl-3H-  
30 1H-imidazo[4,5-c]pyridin-7-yl]oxy)ethyl)-4-thiomorpholinecarboxylate

To a solution of the compound of Example 3(c) (0.35 g, 1.4 mmol) and carbon tetrabromide (0.46 g, 1.4 mmol) in methylene chloride (4 mL) was added drop wise a solution of triphenylphosphine (0.38 g, 1.4 mmol) in methylene chloride (2.5 mL). After 1 h at room temperature, the mixture was filtered and the filtrate  
35 was added to a mixture of the compound of intermediate VII (200 mg, 0.70 mmol) and cesium carbonate (325 mg, 1.0 mmol) in DMF (5 mL). After 18 h, the reaction mixture was partitioned between water and ethyl acetate. The organic extracts

were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (50 to 100% EtOAc/hexanes, silica gel) to give 0.24 g of the desired compound. MS (ES+) m/z 510.3 (M+H)<sup>+</sup>.

5

e) 1,1-Dimethylethyl 3-(2-[[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-4-(3-hydroxy-3-methyl-1-butyn-1-yl)-1H-imidazo[4,5-c]pyridin-7-yl]oxy]ethyl)-4-thiomorpholinecarboxylate

A mixture of the compound of Example 3(d) (225 mg, 0.44 mmol), 2-methyl-3-butyn-2-ol (0.112 ml, 1.3 mmol), triethylamine (94 uL), DBU (98 uL), zinc dust (5 mg), NaI (10 mg), and (Ph<sub>3</sub>P)<sub>4</sub>Pd (25 mg) in DMSO (3 mL) was heated at 100 °C under argon in a sealed tube for 6 h. The reaction was cooled to ambient temperature, diluted with water and extracted with ethyl acetate. The combined organic extracts were sequentially washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (50 to 100% EtOAc/hexanes, silica gel) gave 0.14 g of the desired compound. MS (ES+) m/z 558.4 (M+H)<sup>+</sup>.

10

f) 4-(2-(4-Amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[[2-(3-thiomorpholinyl)ethyl]oxy]-1H-imidazo[4,5-c]pyridin-4-yl)-2-methyl-3-butyn-2-ol

To the compound of Example 3(e) (120 mg, 0.21 mmol) was added 20% TFA in methylene chloride (5 ml) at room temperature. After 20 min., the solution was diluted with ethyl acetate (15 mL) and water (5 mL). The solution was adjusted to pH 8 with 6 N NaOH and the resulting precipitate was isolated by filtration. The precipitated was then dissolved in hot ethanol and a solution of 4 N HCl in dioxane (90 uL) was added. The final precipitate was collected by filtration and dried under vacuum to afford 75 mg of the title compound. MS (ES+) m/z 458.5 (M+H)<sup>+</sup>.

15

20

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#### Example 4 - Capsule Composition

30

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

INGREDIENTS

AMOUNTS

4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-pyrrolidiny]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol, bis-trifluoroacetic acid salt	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 5 - Injectable Parenteral Composition

5 An injectable form for administering the present invention is produced by stirring 1.5% by weight of 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-piperidiny]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol, dihydrochloride, in 10% by volume propylene glycol in water.

Example 6 - Tablet Composition

10

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.

15

Table II

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
4-(2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-{{2-(3-thiomorpholinyl)ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl)-2-methyl-3-butyn-2-ol	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

20

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

What is claimed is:

1. A compound selected from:

5

4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-pyrrolidinyl]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol;

4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-({2-[(2S)-2-piperidinyl]ethyl}oxy)-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol; and

10

4-(2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-{{2-(3-thiomorpholinyl)ethyl}oxy})-1H-imidazo[4,5-c]pyridin-4-yl]-2-methyl-3-butyn-2-ol;

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

15

2. A pharmaceutical composition comprising a compound according to claim 1, and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof and a pharmaceutically acceptable carrier.

20

3. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier and an effective amount of a compound of claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof, which process comprises bringing the compound of claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof into association with a pharmaceutically acceptable carrier.

25

4. 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 of claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof.

30

5. The method of claim 4 wherein the mammal is a human.

35

6. The method according to claim 4 wherein said 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.

7. Use of a compound of claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof, in the manufacture of a medicament for use in treating or lessening the severity of a disease or condition selected from cancer and arthritis.

8. The method of inhibiting Akt activity in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof.

9. The method of claim 8 wherein the mammal is a human.

10. A method of treating cancer in a mammal in need thereof, which comprises: co-administering to such mammal a therapeutically effective amount of

- a) a compound of claim 1 and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof; and
- b) at least one anti-neoplastic agent.

11. The method claim 10, wherein the at least one anti-neoplastic agent is selected from the group consisting essentially of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

12. The method of claim 10, wherein the at least one anti-neoplastic agent is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

13. The method of claim 10, wherein the at least one anti-neoplastic agent is a diterpenoid.

14. The method of claim 10, wherein the at least one anti-neoplastic agent is a vinca alkaloid.

15. The method of claim 10, wherein the at least one anti-neoplastic agent is a platinum coordination complex.

5 16. The method of claim 10, wherein the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

17. The method of claim 10, wherein the at least one anti-neoplastic agent is paclitaxel.

10 18. The method of claim 10, wherein the at least one anti-neoplastic agent is carboplatin.

15 19. The method of claim 10, wherein the at least one anti-neoplastic agent is vinorelbine.

20. The method of claim 10, wherein the at least one anti-neoplastic agent is a signal transduction pathway inhibitor.

20 21. The method of claim 20, wherein the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase selected from the group consisting of VEGFR2, TIE2, PDGFR, BTK, IGFR-1, TrkA, TrkB, TrkC, and c-fms.

25 22. The method of claim 20, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of rafk, akt, and PKC-zeta.

30 23. The method of claim 20, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the src family of kinases.

24. The method of claim 23, wherein the signal transduction pathway inhibitor is an inhibitor of c-src.

35 25. The method of claim 20, wherein the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

26. The method of claim 20, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.
- 5 27. The method of claim 10, wherein the at least one anti-neoplastic agent is a cell cycle signaling inhibitor.
28. The method of claim 27, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.
- 10 29. A pharmaceutical combination as claimed in claim 10 for use in therapy.
30. The use of a pharmaceutical combination as claimed in claim 10 for  
15 the preparation of a medicament useful in the treatment of cancer.