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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HEERDING, Dirk, A.** [NL/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **LIN, Hong** [CN/US]; 1250 South Collegeville Road, Collegeville, PA 19406 (US). **YAMASHITA, Dennis, A.** [US/US]; 531 Walker Road, Wayne, PA 19087 (US).

(74) Agents: **DUSTMAN, Wayne, J.** et al.; Glaxosmithkline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: INHIBITORS OF AKT ACTIVITY

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

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INHIBITORS OF Akt ACTIVITY

FIELD OF THE INVENTION

This invention relates to novel substituted pyridine 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

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

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

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell,* 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science,* 275:628-630 (1997); Dudek et al., *Science,* 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell,* 81:727-736 (1995); Hemmings

Science, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB 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, e*t 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/ PKBα, Akt2/PKBβ, and Akt3/PKBγ 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/PKBα occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} 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/PKBβ and Akt3/PKBγ. 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. It is demonstrated in vitro that rictor-mTOR complex phosphorylates AKT on Ser^{473} (Sabbatini et al. *Science* **309**, 1098-1101 (18 Feb 2005)).

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 PdtIns(3,4,5)- P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

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

Small molecule inhibitors of Akt are useful in the treatment of tumors, especially those with activated Akt (e.g. PTEN null tumors and tumors with ras mutations). PTEN is a critical negative regulator of Akt and its function is lost in many cancers, including breast and prostate carcinomas, glioblastomas, and several cancer syndromes including Bannayan-Zonana syndrome (Maehama, T. *et al. Annual Review of Biochemistry*, *70*: 247 (2001)), Cowden disease (Parsons, R.; Simpson, L. *Methods in Molecular Biology (Totowa, NJ, United States)*, *222 (Tumor Suppressor Genes, Volume 1)*: 147 (2003)), and Lhermitte-Duclos disease

(Backman, S. *et al. Current Opinion in Neurobiology*, *12(5)*: 516 (2002)). Inhibition of Akt has also been implicated in the treatment of leukemias, (J.C. Byrd, S. Stilgenbauer and I.W. Flinn "Chronic lymphocytic leukemia." Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program (2004), 163-83). 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)). Activating pH-domain mutant of AKT1 has been identified in 8% of breast cancer, 6% of colorectal cancer and 2% of ovarian cancer (Carpten et al. *Nature* **448**, 439-444 (04 Jul 2007)). Therefore a small molecule Akt inhibitor is expected to be useful for the treatment of these types of cancer as well as other types of cancer. Akt inhibitors are also useful in combination with further chemotherapeutic agents.

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

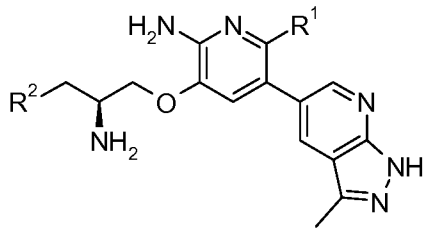
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

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):



(I)

wherein:

R^1 is 2-methyl-3-furanyl; and

R^2 is selected from the group consisting of: phenyl and phenyl substituted with from one to three fluorine substituents;

and/or pharmaceutically acceptable salts thereof.

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).

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).

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

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

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

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

International Application No. PCT/US2005/006711, having an International filing date of March 2, 2005; International Publication Number WO 2005/085227 and an International Publication date of September 15, 2005, the schemes, processes and assays of which are hereby incorporated by reference, discloses and claims substituted pyridine 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/US2005/006711 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/US2005/006711.

While the compounds of International Application No. PCT/US2005/006711 are useful as inhibitors of serine/threonine kinase, AKT (also known as protein kinase B), the compounds of Formula (I) generally exhibit advantageous properties which overall render them advantageous over what is considered to be the most structurally related compounds disclosed in International Application No. PCT/US2005/006711.

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 those wherein:

R^1 is 2-methyl-3-furanyl; and

R^2 is selected from the group consisting of: phenyl and phenyl substituted with one or two fluorine substituents;

and/or pharmaceutically acceptable salts thereof.

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

R^1 is 2-methyl-3-furanyl; and

R^2 is selected from the group consisting of: phenyl and phenyl substituted with one or three fluorine substituents;

and/or pharmaceutically acceptable salts thereof.

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

3-{[(2S)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinamine; and

3-{[(2S)-2-amino-3-(2,3,4-trifluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinamine;

and/or pharmaceutically acceptable salts thereof.

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

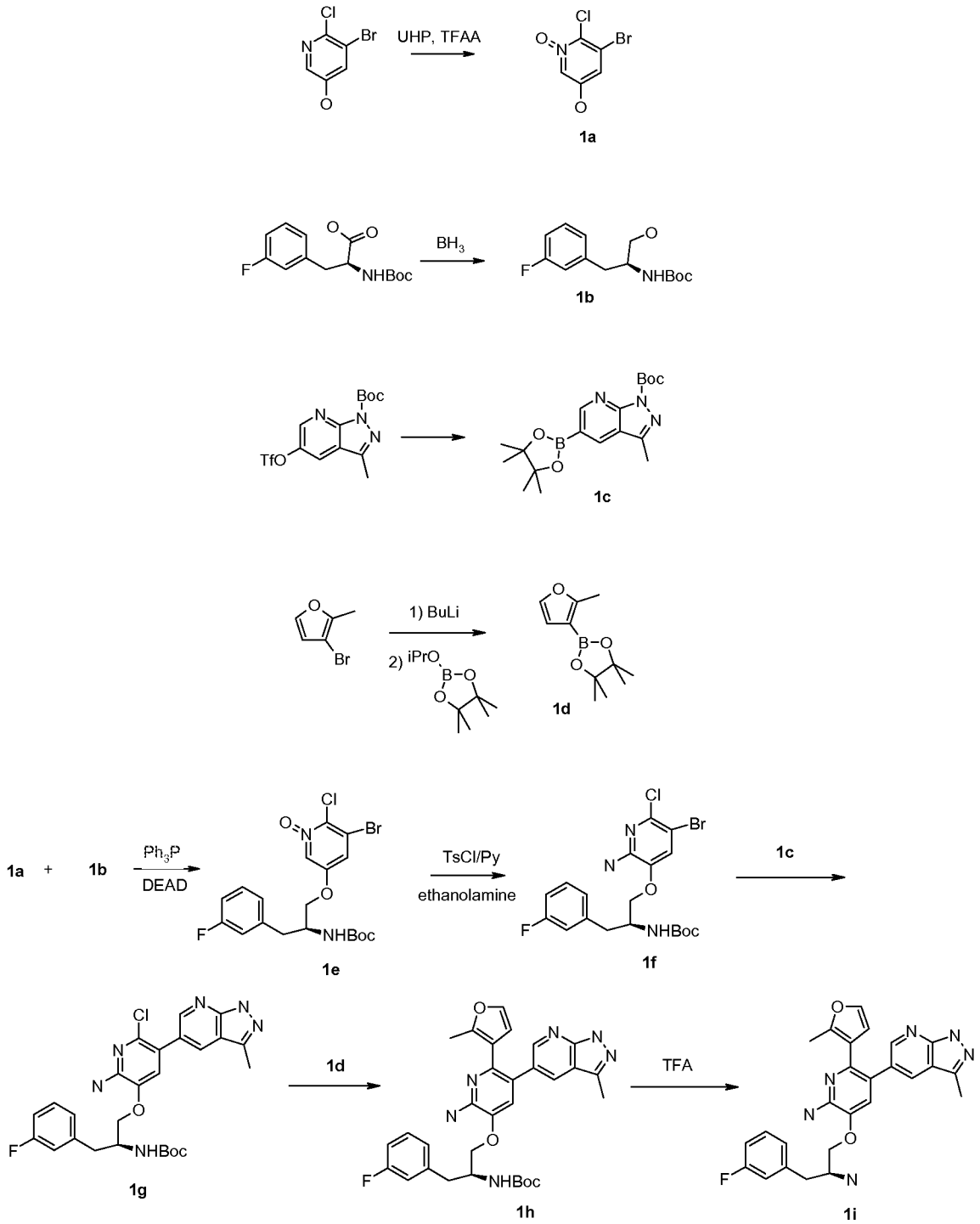
Unless otherwise stated, the compounds disclosed herein also include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within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

By the term "treating" and derivatives thereof as used herein, is meant prophylatic and therapeutic therapy. Prophylactic therapy is appropriate, for example, when a subject is considered at high risk for developing cancer, or when a subject has been exposed to a carcinogen.

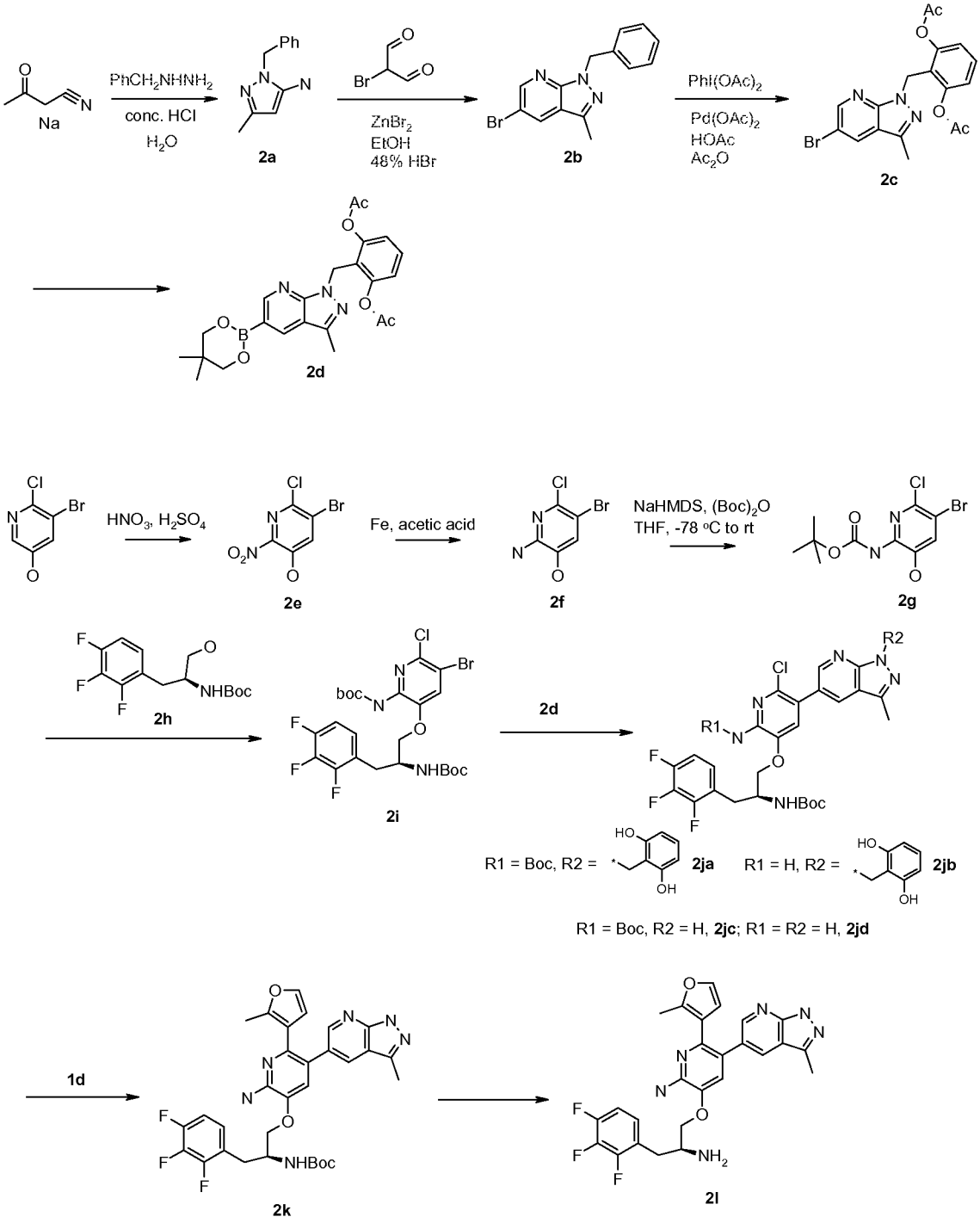
As used herein, the term "effective amount" and derivatives thereof means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term “therapeutically 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 Schemes 1 and 2 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.

Scheme 1


UHP, TFAA
1a
BH3
1b
1c
1) BuLi
2) iPrO
1d
1a + 1b
Ph3P
DEAD
1e
TsCl/Py
ethanolamine
1f
1c
1d
TFA
1g
1h
1i

Scheme 2



Pyridine N-oxide **1a** can be prepared from oxidation of 2-chloro-3-bromo-5-hydroxy-pyridine (ref. *Synthesis* **1990**, 499-501) using urea hydrogen peroxide complex and trifluoroacetic anhydride. Ethers such as **1e** can be prepared by Mitsunobu coupling with hydroxy-pyridines such as **1a** and alcohols such as 1,1-dimethylethyl [(1*S*)-2-(3-fluorophenyl)-1-(hydroxymethyl)ethyl]carbamate (**1b**), which can be prepared from a BH_3 reduction of an acid precursor (Scheme 1). An

amino group can be introduced to the 2-position of the pyridine core by ethanolamine breaking down the 2-pyridinium intermediate, which can be prepared from N-oxide **1e** using TsCl and pyridine as the solvent. The regioisomer, 4-amino by-product can be separated. An aryl moiety such as a 6-(3-methyl-pyrazolopyridine) can be selectively introduced by stoichiometric use of the Suzuki reaction (Pd-mediated cross coupling between aryl boronic acids or aryl boronic esters to aryl halides or triflates, some of aryboronic esters can be prepared from aryl halides or triflates using Pd (0) catalysts and biborinanes such as 4,4,4',4'-tetramethyl-1,1'-biborinane (see **1c**), while some of them such as **1d** can be prepared by quenching lithiated methylfuran with borolanes such as 4,4,5,5-tetramethyl-2-[(1-methylethyl)oxy]-1,3,2-dioxaborolane, Chem Rev, 1995, 95(7), 2457-83) or a Stille reaction (Pd-mediated cross coupling between aryltrialkylstannanes and aryl halides or triflates, (Angewandte Chemie, International Edition 2004, 43(36), 4704-4734) to produce intermediates such as **1g** (Scheme 1). A second aryl moiety such as a methylfuran group can be introduced at the adjacent position on the pyridine by a second Suzuki or Stille reaction forming trisubstituted pyridines such as **1i** (Scheme 1), followed by deprotection steps.

An alternative method (Scheme 2) to make the pyrazolopyridine moiety such as **2b** is to condense bromopropanedial and a 2-aminopyrazole such as **2a**, which can be prepared from cyclization of (phenylmethyl)hydrazine with 3-oxobutanenitrile sodium salt. De-benzylation is non-trivial in this case. However, an unprecedented C-H activation (Dick, Allison R.; Hull, Kami L.; Sanford, Melanie S. A highly selective catalytic method for the oxidative functionalization of C-H bonds. *Journal of the American Chemical Society* (**2004**), 126(8), 2300-2301) allows introduction of two acetoxy groups in the benzene ring, which facilitates the deprotection of the substituted benzyl group under basic conditions in the later steps.

On the other hand, 2-amino group can be introduced from region selective nitration of 2-chloro-3-bromo-5-hydroxy-pyridine followed by reduction of nitro group to afford **2f**. 2-Amino group can be protected using Boc_2O. Subsequent Mitsunobu coupling, and two Suzuki coupling followed by deprotection steps can also provide final compounds such as **2l**.

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), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Examples of a further active ingredient or ingredients (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.

Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G_2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding

with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

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

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

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

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

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

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosupression and gastrointestinal mucositis effects occur.

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

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

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

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

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

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

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

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

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

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

Delayed myelosuppression is the most common dose limiting side effects of carmustine.

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

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

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

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

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

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular

carcinomas. Pulmonary and cutaneous toxicities are the most common dose limiting side effects of bleomycin.

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

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

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

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

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

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

side effects of 5-fluorouracil. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

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

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

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

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

Methotrexate, N-[4[[(2,4-diamino-6-pteridinyl) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis,

repair and/or replication through the inhibition of dyhydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

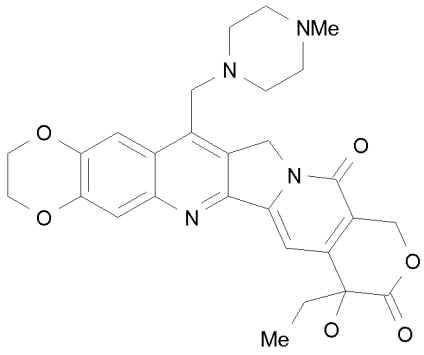
Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan,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

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

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

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

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



A

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

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) 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 tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

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

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

“EGFR”, also known as “erbB-1”, and “erbB-2” are protein tyrosine kinase transmembrane growth factor receptors of the erbB family. Protein tyrosine kinases

catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge, Dev. Supp.l, 1993, 57-64; J.A. Cooper, Semin. Cell Biol., 1994, 5(6), 377-387; R.F. Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394-401). The ErbB family of type I receptor tyrosine kinases includes ErbB1 (also known as the epidermal growth factor receptor (EGFR or HER1)), erbB2 (also known as Her2), erbB3, and erbB4. These receptor tyrosine kinases are widely expressed in epithelial, mesenchymal, and neuronal tissues where they play a role in regulating cell proliferation, survival, and differentiation (Sibilia and Wagner, *Science*, 269: 234 (1995); Threadgill et al., *Science*, 269: 230 (1995)). Increased expression of wild-type erbB2 or EGFR, or expression of constitutively activated receptor mutants, transforms cells *in vitro* (Di Fiore *et al*., 1987; DiMarco et al, *Oncogene*, 4: 831 (1989); Hudziak et al., *Proc. Natl. Acad. Sci. USA*., 84:7159 (1987); Qian et al., *Oncogene*, 10:211 (1995)). Increased expression of erbB2 or EGFR has been correlated with a poorer clinical outcome in some breast cancers and a variety of other malignancies (Slamon et al., *Science*, 235: 177 (1987); Slamon et al., *Science*, 244:707 (1989); Bacus et al, *Am. J. Clin. Path*, 102:S13 (1994)).

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, the active compound known as lapatanib and Tykerb®, is an inhibitor of both erbB-1 and erbB-2. Suitably, N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine is used in combination with a compound of the present invention.

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 tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit,

Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.

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

Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku 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) 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 Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

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

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kniases, Breast cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

Non-receptor kinase angiogenesis inhibitors may also 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 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 ($alpha_v$ $beta_3$) 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 thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

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

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

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

Suitably, the invention relates to a method of treating cancer in a mammal, including a human, wherein the cancer is selected from: malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma and follicular lymphoma.

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

Suitably, the invention relates to a method of treating pre-cancerous syndromes in a mammal, including a human, wherein the pre-cancerous syndrome is selected from: myelodysplastic syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithleial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis (especially viral induced hepatitis) which can progress to cancer.

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

Insect cells expressing His-tagged AKT1 (aa 136-480) were lysed in 25 mM HEPES, 100 mM NaCl, 20 mM imidazole; pH 7.5 using a polytron (5 mLs lysis buffer/g cells). Cell debris was removed by centrifuging at 28,000 x *g* for 30 minutes. The supernatant was filtered through a 4.5-micron filter then loaded onto a nickel-chelating column pre-equilibrated with lysis buffer. The column was washed with 5 column volumes (CV) of lysis buffer then with 5 CV of 20% buffer B, where buffer B is 25 mM HEPES, 100 mM NaCl, 300 mM imidazole; pH 7.5. His-tagged AKT1 (aa 136-480) was eluted with a 20-100% linear gradient of buffer B over 10 CV. His-tagged AKT1 (136-480) eluting fractions were pooled and diluted 3-fold with buffer C, where buffer C is 25 mM HEPES, pH 7.5. The sample was then chromatographed over a Q-Sepharose HP column pre-equilibrated with buffer

C. The column was washed with 5 CV of buffer C then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl; pH 7.5. His-tagged AKT1 (aa 136-480) containing fractions were pooled and concentrated in a 10-kDa molecular weight cutoff concentrator. His-tagged AKT1 (aa 136-480) was chromatographed over a Superdex 75 gel filtration column pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 1 mM DTT; pH 7.5. His-tagged AKT1 (aa 136-480) fractions were examined using SDS-PAGE and mass spec. The protein was pooled, concentrated and frozen at –80C.

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

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 the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation was detected by the following procedure:

Assays were performed in 384well U-bottom white plates. 10 nM activated AKT enzyme was incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM $MgCl_2$, 4uM ATP, 8uM peptide, 0.04 uCi [g-^{33}P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction was stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate was sealed, the beads were allowed to settle overnight, and then the plate was counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses were plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound

where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: y = ((Vmax * x) / (K + x)) where Vmax is the upper asymptote and K is the IC50.

Cloning of full-length human (FL) AKT1:

Full-length human AKT1 gene was amplified by PCR from a plasmid containing myristylated-AKT1-ER (gift from Robert T. Abraham, Duke University under MTA, described in Klippel et al. in Molecular and Cellular Biology 1998 Volume 18 p.5699) using the 5' primer: SEQ. ID NO: 2 5' TATATAGGATCCATGAGCGACGTGGC 3' and the 3' primer: SEQ. ID NO: 3 AAATTTCTCGAGTCAGGCCGTGCTGCTGG 3'. The 5' primer included a BamHI site and the 3'primer included an XhoI site for cloning purposes. The resultant PCR product was subcloned in pcDNA3 as a BamHI / XhoI fragment. A mutation in the sequence (TGC) coding for a Cysteine^{25} was converted to the wild-type AKT1 sequence (CGC) coding for an Arginine^{25} by site-directed mutagenesis using the QuikChange® Site Directed Mutagenesis Kit (Stratagene). The AKT1 mutagenic 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 (Invitrogen).

Expression of FL human AKT1:

Expression was done using the BAC-to-BAC Baculovirus Expression System from 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 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 buffer C (25 mM HEPES, 5 mM DTT; pH 7.5). The sample was filtered and chromatographed over a 10 mL Q-HP column pre-equilibrated with buffer C at 2 mL/min.

The Q-HP column was washed with 3 column volume (CV) of buffer C, then step 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 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.

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

Full-Length AKT Enzyme Assay

Compounds of the present invention were tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use

the catalytic domains of AKT 1, 2, or 3. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation was detected by the following procedure.

Assays were performed in 384well U-bottom white plates. 10 nM activated AKT enzyme was incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM MgCl2, 4uM ATP, 8uM peptide, 0.04 uCi [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 (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate was sealed, the beads were allowed to settle overnight, and then the plate was counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT). The data for dose responses were plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: $y = ((Vmax * x) / (K + x))$ where Vmax is the upper asymptote and K is the IC50.

Compounds of the invention are tested for activity in the above referenced assays.

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

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring AKT inhibition, which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt 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. Suitably, the mode of administration is intravenous.

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 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, for example, 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.

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

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

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.

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.

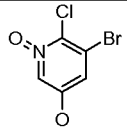
Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in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

Experimental Details

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

Example 1

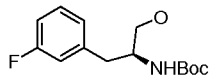
Synthesis of 3-{[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-pyridinamine



1a

a) 5-Bromo-6-chloro-3-pyridinol *N*-Oxide

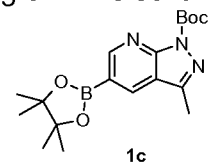
Trifluoroacetic anhydride (120 g, 84ml, 0.6mol, 2eq) was added slowly to a mixture of 5-bromo-6-chloro-3-pyridinol (ref. *Synthesis* **1990**, 499-501) (62.4g, 0.3 mol),urea hydrogen peroxide (59g, 0.63 mol, 2.1eq) and 1L anhydrous CH_2Cl_2 at 0 °C. The reaction mixture was stirred at rt for 2h and the reaction was completed indicated by TLC (50% ethylacetate in hexane). The reaction was quenched with 0.1N $Na_2S_2O_3$ aq. solution (1.5L) and the resulting mixture was stirred for 1h. The precipitate was collected by filtration, washed with 1L water followed by 300 mL of hexane and the solid was dried under vacuum to give 59.3g of off white product **1a** (88%).



1b

b) 1,1-dimethylethyl [(1*S*)-2-(3-fluorophenyl)-1-(hydroxymethyl)ethyl]carbamate

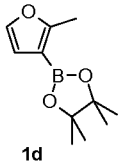
Boc-L-3-fluorophenylalanine (1.0g, 3.5 mmol)) was dissolved in dry THF (15ml) at 0 °C under N_2. BH_3 (1M in THF, 9.6ml) was added dropwise. The reaction was stirred for 30 min before it was warmed up to rt. Methanol was added to quench the excess BH_3. The mixture was washed with brine, dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified on Biotage (30% EtOAc/hexane) to give 0.66g of white solid **1b** (70%).



1c

c) 1,1-dimethylethyl 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate

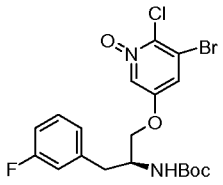
A mixture of 1,1-dimethylethyl 3-methyl-5-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (ref. PCT Int. Appl. (**2005**), WO 2005085227) (1.3g, 3.41 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.13g, 4.43 mmol), potassium acetate (0.5g, 5.11 mmol), Pd(dppf)Cl_2 CH_2Cl_2 (140mg, 0.17 mmol) and dioxane (20 mL) was charged into a 50 ml sealed flask. The reaction was heated at 80 °C for 4 hours. The reaction mixture was filtered and the solvent was removed under vacuum. The residue was purified on Biotage (30% EtOAc/hexane) to give 0.62g of **1c** as a white solid (50%).



1d

d) 4,4,5,5-tetramethyl-2-(2-methyl-3-furanyl)-1,3,2-dioxaborolane

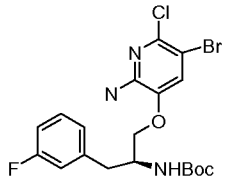
To a 1 liter 3-neck round-bottomed flask was added 280 mL of anhydrous THF under nitrogen. This mixture was cooled to -40 °C (internal temperature with a thermometer). To this was added nBuLi (2.5 M in hexane, 75 mL, 187.5 mmol, 1.2 equiv). The mixture was then cooled to between -65 to -70 °C. Neat 3-bromo-2-methylfuran (ref. *Tetrahedron,* Vol. 52, No. 11, pp. 4065-4078, **1996**) (25.0 g, 155.3 mmol, 1 equiv) was added dropwise over a period of 25 min. After 20 min at -70 °C, the isopropoxyl boronate (36 g, 193.5 mmol, 1.25 equiv) was added. The temperature was maintained between -55 and -60 °C. Addition was completed over a 10 min period. The cooling bath was removed, and the mixture was warmed up to 0 °C, to which was added 100 mL of cold 2N aq HCl, and the pH of the resulting mixture was 3. A few drops of 1N NaOH were added to adjust pH to 6. To the mixture was added solid NaCl to saturate the aq phase. The mixture was extracted with 2 x 250 mL of TBME. The combined organic was dried over Na_2SO_4, filtered, and concentrate in vacuo to give an oil (48 g), which was combined with the product (38 g) from another run (from 20.73 g of 3-bromo-2-methylfuran). The resulting material was purified by silica gel column chromatography using gradient elution of of 1% of CH_2Cl_2 in hexane, followed by 5%, 10%, 15% etc. The 1%, 5-25% fractions were combined and conc in vacuo to give 53.30 g of **1d**. (Note: **1d** is volatile; boiling point is estimated at 55-57 C at 2 torr. Therefore, this compound can be purified by distillation).



1e

e) 1,1-dimethylethyl {(1*S*)-2-[(5-bromo-6-chloro-1-oxido-3-pyridinyl)oxy]-1-[(3-fluorophenyl)methyl]ethyl}carbamate

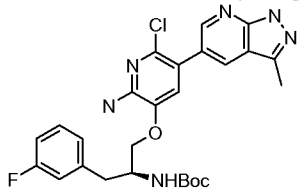
DEAD (0.44 mL, 2.45 mmol) was added to a solution of **1a** (370 mg, 1.63 mmol), **1b** (0.66 g, 2.45 mmol) and Ph_3P (640mg, 2.45 mmol) in THF (15 mL)/DMF (5 mL) at rt. The resulting mixture was stirred for 2 h. The solvents were removed under vacuum and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc 1:1) to give 600 mg (77%) of **1e**.



1f

f) 1,1-dimethylethyl {(1*S*)-2-[(2-amino-5-bromo-6-chloro-3-pyridinyl)oxy]-1-[(3-fluorophenyl)methyl]ethyl}carbamate

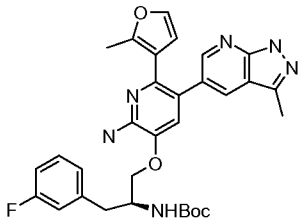
A mixture of **1e** (600 mg, 1.26 mmol), TsCl (600 mg, 2.5 eq.), and pyridine (10 mL) was stirred at rt for 2 h. The reaction was completed indicated by LCMS. The reaction mixture was concentrated under high vacuum to dryness and the residue was dissolved in ethanolamine (10 mL). The reaction mixture was stirred at rt for 2 hr. Water was added, the solid was collected and purified by flash column chromatography on silica gel (hexane/EtOAc 3:1) to give 240 mg (44%) of **1f**.



1g

g) 1,1-dimethylethyl {(1*S*)-2-{[2-amino-6-chloro-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-3-pyridinyl]oxy}-1-[(3-fluorophenyl)methyl]ethyl}carbamate

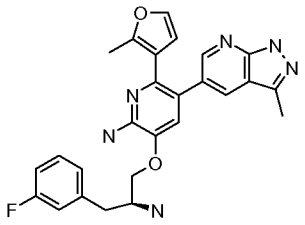
A mixture of **1f** (260 mg, 0.55 mmol), **1c** (300 mg, 1.5 eq.), $Pd(dppf)Cl_2$•DCM(22mg, 5 mol%), Na_2CO_3 (2N, 0.60 mL) and dioxane (6 ml) was degassed with N_2, sealed and irradiated with MW at 150 °C for 30 min. LC/MS showed 20% of starting material remaining. Another 60 mg of **1c**, 0.12 mL of 2N Na_2CO_3 and 10 mg of Pd catalyst were added. The resulting mixture was degassed with N_2, sealed and irradiated with MW at 150 °C for 10 min. The reaction mixture was filtered and rinsed with EtOAc. The combined filtrates were concentrated and the residue was purified by flash column chromatography on silica gel (50% H/E) to give 200 mg (69%) of **1g**.



1h

h) 1,1-dimethylethyl {(1*S*)-2-{[2-amino-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-3-pyridinyl]oxy}-1-[(3-fluorophenyl)methyl]ethyl}carbamate

A mixture of **1g** (140 mg, 0.26 mmol), **1d** (140mg, 0.6 mmol), Na_2CO_3 (2N, 0.33 ml) and $Pd(dppf)Cl_2$ CH_2Cl_2 (11mg, 0.013 mmol) in dioxane (3ml) was charged into a sealed tube and was microwave irradiated at 160 °C for 20 min. The reaction mixture was filtered and washed with EtOAc. The solvent was removed under vacuum and the residue was purified on Biotage (50% H/E) to give 75 mg (50%) product **1h.**



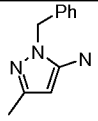
1i

i) 3-{[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-pyridinamine

1h (75 mg, 0.13 mmol) was dissolved in DCM (5ml), and TFA (2mL) was added. The mixture was stirred at rt for 30 min. The solvent was removed under vacuum and the residue was purified by reverse phase HPLC (10% org ~ 60% org) to give 50 mg of **1i** as a TFA salt, which was then converted into an HCl salt using 2N HCl aqueous solution. LC-MS: M+H = 473.2; HNMR (d-MeOH, 400 MHz) □ 8.40 (s, 1H), 8.37 (s, 1H), 7.74 (s, 1H), 7.50~7.05 (m, 5H), 6.47 (d, *J* = 2 Hz, 1H), 4.55-4.40 (m, 2H), 4.15-4.05 (m, 1H), 3.25-3.23 (m, 2H), 2.61 (s, 3H), 1.94 (s, 3H).

Example 2

Synthesis of 3-{[(2*S*)-2-amino-3-(2,3,4-trifluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-pyridinamine

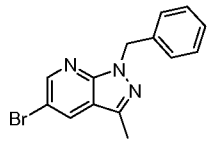


2a

a) 3-Methyl-1-(phenylmethyl)-1*H*-pyrazol-5-amine

To (phenylmethyl)hydrazine (100g, 0.513mol) in 220ml of H_2O at 70 °C was added 3-oxobutanenitrile sodium salt (48.62g, 0.463mol) in one portion, and then 110 ml of H_2O and 177ml of the conc. HCl . The reaction mixture was heated at 105 °C for 30mins. LC/MS showed product. The reaction mixture was cooled to rt, then chilled in ice-water bath, and pH was adjusted to 6 using 50%w NaOH. A waxy

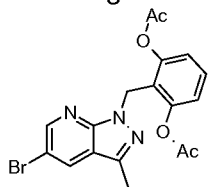
solid was collected. To this solid was added EtOAc (50ml) and hexane (100ml). The resulting solution was cooled at -20 °C to give 12.0g solid (14% yield). The mother liquid was concentrated and purified by silica gel column (3/10/0.5(v/v/v)=EtOAc/ DCM/MeOH) to give 38.6g of **2a** as a solid (45%).



2b

b) 5-Bromo-3-methyl-1-(phenylmethyl)-1*H*-pyrazolo[3,4-*b*]pyridine

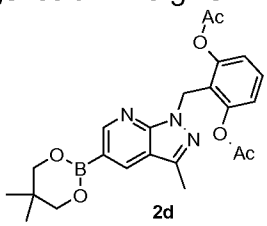
To a solution of 3-methyl-1-(phenylmethyl)-1*H*-pyrazol-5-amine (27.6g, 0.147mole), $ZnBr_2$ (0.2eq, 6.62g), 48% HBr (14ml) in 210 mL of EtOH was added bromopropanedial (27g, 0.258mole). The reaction mixture was heated at 90 °C for 2h. Another portion of bromopropanedial (12g, 0.079mole) was added and the resulting mixture was heated for another 90 min . The reaction mixture was cooled to rt and then chilled at 0 °C to give 22.42g of **2b** as a crystal (50%).



2c

c) 2-[(5-Bromo-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)methyl]benzene-1,3-diyl diacetate

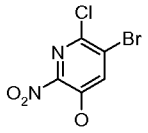
A mixture of 5-bromo-3-methyl-1-(phenylmethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.24g, 20.65mmol), bis(acetyloxy)(phenyl)-□^{3}-iodane (16.4g, 50.92mmol), $Pd(OAc)_2$ (440mg, 1.96mmole), 135mL of HOAc and 15ml of Ac_2O was heated at 100 °C for 18hr. The reaction mixture was cooled to rt and then concentrated in vacuo before purified on silica gel column to give 7.70g of **2c** as a solid (89%)



2d

d) 2-{[5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl]methyl}benzene-1,3-diyl diacetate

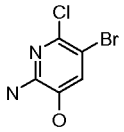
The title compound was prepared following procedure 1(c) except substituting 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane with 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane.



2e

e) 5-Bromo-6-chloro-2-nitro-3-pyridinol

To a 500 mL 3-neck flask was added sulfuric acid (30 mL, 98%) at *ca*. 0 °C, followed by portion-wise addition of 5-bromo-6-chloro-3-pyridinol (10.0 g, 48.1 mmol). After 75 min, a mixture of conc. sulfuric acid (98%) and fuming nitric acid (8 mL, 5:3 ratio) was added *via* dropping funnel to the stirring dark red contents over a 5 min period. After 2 h stirring at *ca*. 0 °C, the contents were removed from ice-bath, and stirred with warming to room temperature. After 16 h, the dark red-orange mixture was slowly poured onto 600 g ice-water (2:1), and the resulting heterogenous yellow mixture stirred for 60 min. The precipitated solid was suction-filtered on a fritted funnel, and the filter cake was washed with water. The collected solid was taken up in EtOAc (75 mL) and washed with brine (25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a pale orange solid which was vacuum dried to yield 7.93 g (65%) of **2e**. ^{1}H NMR: (DMSO-d_6) □ 8.04 (s, 1H); phenolic proton does not appear.

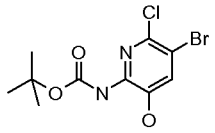


2f

f) 2-Amino-5-bromo-6-chloro-3-pyridinol

To a 500 mL 3-neck flask equipped with mechanical stirrer was added glacial acetic acid (70 mL, 98%), followed by portion-wise addition of 5-bromo-6-chloro-2-nitro-3-pyridinol (7.9 g, 31.2 mmol). Iron powder (8.86 g, 158.6 mmol) was added in portions over a 10 min period to the stirring mixture. After 30 min, additional iron powder was added (5.32 g, 95.2 mmol) to the stirring dark olive green contents. After 25 min, the contents became brown-orange colored and an exotherm was observed (ice bath used for 5 min). The reaction mixture was stirred at room temperature for another 80 min, after which time the thick gray colored contents were diluted with EtOAc (100 mL) and filtered on a pad of Celite®. The filter cake was washed with additional EtOAc (100mL). The combined filtrates were concentrated to yield a black solid that was quickly purified on a pad of silica gel, eluting with 15:1 to 10:1 DCM/MeOH. The title material was isolated as a beige solid (6.75 g, 97% yield). ^{1}H NMR: (DMSO-d_6) ^{1}H NMR: (DMSO-d_6) □ 10.24 (s,

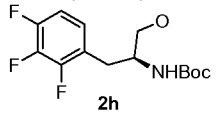
1H), 7.02 (s, 1H), 6.18-6.24 (br s, 2H); LC/MS (MH+) = 222.8, 224.6, RT = 1.31 min.



2g

g) 1,1-Dimethylethyl (5-bromo-6-chloro-3-hydroxy-2pyridinyl)carbamate

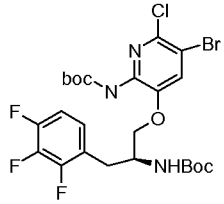
To a 1000 mL 3-neck flask was added THF (200 mL), followed by 2-amino-5-bromo-6-chloro-3-pyridinol (4.2 g, 19.7 mmol), and the mixture cooled to -72 °C with stirring. Added next was NaHMDS (1.0 M solution in THF, 59.1 mL, 59.1 mmol) *via* dropping funnel over a 50 min period, keeping the temperature below -65 °C. After 15 min, a 27 mL THF solution of *tert*-butyloxycarbonyl anhydride (4.3 g, 19.7 mmol) was added *via* dropping funnel over a 40 min period, keeping the temperature below -65 °C. The contents were removed from cold bath and stirred over a 3 h period. The dark colored mixture was poured onto a stirring ice-water mixture (300 g, 1:1) and adjusted to pH = 6-7 by slow addition of 175 mL 1 N HCl, keeping the temperature below 5 °C. The cold mixture was extracted with EtOAc (3 x 150 mL), combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a thick brown oil. The crude product was purified by silica gel chromatography (eluent: 9:1 Hex/EtOAc) to afford the title compound as a fine light yellow solid, 4.8 g (79%). ^{1}H NMR: (DMSO-d_6) □ 10.71 (s, 1H), 9.07 (s, 1H), 7.52 (s, 1H), 1.44 (s, 9H); LC/MS (MH+) = 322.7, 324.8; RT = 2.26 min.



2h

h) 1,1-dimethylethyl {(1*S*)-2-hydroxy-1-[(2,3,4-trifluorophenyl)methyl]ethyl}carbamate

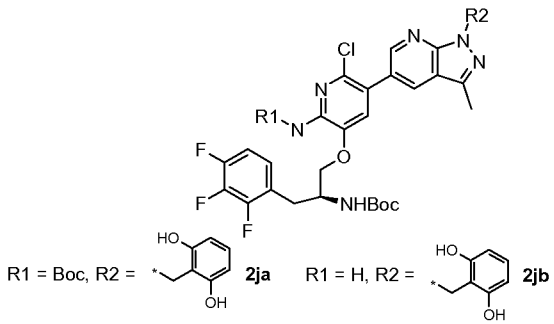
The title compound was prepared following procedure 1(c) except substituting Boc-L-3-fluorophenylalanine with Boc-L-3,4.5-trifluorophenylalanine.



2i

i) 1,1-dimethylethyl {(1*S*)-2-{[5-bromo-6-chloro-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-pyridinyl]oxy}-1-[(2,3,4-trifluorophenyl)methyl]ethyl}carbamate

The title compound was prepared following procedure 1(e) except substituting **1b** with **2g**, and **1a** with **2h**.

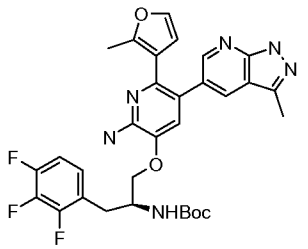


R1 = Boc, R2 = **2ja** R1 = H, R2 = **2jb**

R1 = Boc, R2 = H, **2jc**; R1 = R2 = H, **2jd**

j) 1,1-dimethylethyl {(1*S*)-2-{[6-chloro-5-{1-[(2,6-dihydroxyphenyl)methyl]-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-pyridinyl]oxy}-1-[(2,3,4-trifluorophenyl)methyl]ethyl}carbamate (2ja), 1,1-dimethylethyl {(1*S*)-2-[(2-amino-6-chloro-5-{1-[(2,6-dihydroxyphenyl)methyl]-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}-3-pyridinyl)oxy]-1-[(2,3,4-trifluorophenyl)methyl]ethyl}carbamate (2jb), 1,1-dimethylethyl {(1*S*)-2-{[6-chloro-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-3-pyridinyl]oxy}-1-[(2,3,4-trifluorophenyl)methyl]ethyl}carbamate (2jc) and 1,1-dimethylethyl {(1*S*)-2-{[2-amino-6-chloro-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-3-pyridinyl]oxy}-1-[(2,3,4-trifluorophenyl)methyl]ethyl}carbamate (2jd)

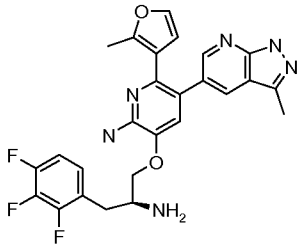
A mixture of **2i** (430 mg, 0.70 mmol), **2d** (320 mg, 0.70 mmol, $Pd(dppf)Cl_2$ DCM adduct (29 mg, 5 mol%), 2N Na_2CO_3 (0.7 mL) and dioxane (dry, 5 mL) in a sealed tube was purged with N_2, sealed and heated at 80 °C for 4 h. To this mixture was added 1N NaOH (3.5 mL, 5 eq.) and the resulting mixture was heated at 100 °C for 1 h. LCMS indicated the completion of the reaction. The reaction mixture was cooled to rt, acidified with HOAc and filtered on celite, which was rinsed with EtOAc. Removal of the solvent followed by flash column chromatography purification on silica gel column afforded 250 mg of **2ja** and **2jb** as a 2:1 mixture, and 170 mg of **2jc** and **2jd** as a 2:1 mixture.



2k

k) 1,1-dimethylethyl {(1*S*)-2-{[2-amino-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-3-pyridinyl]oxy}-1-[(2,3,4-trifluorophenyl)methyl]ethyl}carbamate

A mixture of **2ja** and **2jb** (160 mg, 2:1 mixture), **1d** (146 mg), 2N Na_2CO_3 (0.23 mL), Pd(dppf)Cl_2 DCM adduct (16 mg, 5%) and 1,4-dioxane (dry, 2 mL) in a sealed tube was purged with N_2, sealed and heated at 110 °C for 5 h. NaOH (1N, 5 mL) was added and the resulting mixture was heated at 100 °C overnight. A 2:1 mixture of **2jc** and **2jd** was coupled with **1d** in a same manor as **2ja** and **2jd** without treatment with NaOH. The two reaction mixtures were combined and filtered on celite, which was rinsed with EtOAc. The combined filtrates were concentrated and purified by flash column chromatography on silica gel column (hexane/EtOAc 1:1 to 1:4) to afford 160 mg of **2k**.



2l

l) 3-{[(2*S*)-2-amino-3-(2,3,4-trifluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-pyridinamine

The title compound was prepared following procedure 1i except substituting **1h** with **2k**. HNMR (d-DMSO, 400 MHz) □ 8.33(br, 2H); 8.18(d, 1H, *J*=2.1Hz); 8.05(d, 1H, *J*=2.1Hz);7.56-7.53(m, 2H); 7.36-7.32(m, 2H); 6.27(s, 1H); 4.34-4.31(m, 1H); 4.22-4.21(m, 1H); 4.05-3.98(m, 1H); 3.05(d, 2H, *J*= 7.3Hz); 1.93(s, 3H); MH+= 509.2.

Example 3 - Capsule Composition

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

Table I

INGREDIENTS	AMOUNTS
3-{[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-pyridinamine	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 4 - Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.5% by weight of 3-{[(2*S*)-2-amino-3-(2,3,4-trifluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-pyridinamine, in 10% by volume propylene glycol in water.

Example 5 - Tablet Composition

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

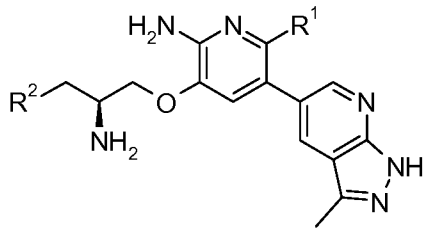
Table II

INGREDIENTS	AMOUNTS
3-{[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-pyridinamine	20 mg
calcium sulfate dehydrate	30 mg
Sucrose	4 mg
Starch	2 mg
Talc	1 mg
stearic acid	0.5 mg

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

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

R^1 is 2-methyl-3-furanyl; and

R^2 is selected from the group consisting of: phenyl and phenyl substituted with from one to three fluorine substituents;

and/or pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein:

R^1 is 2-methyl-3-furanyl; and

R^2 is selected from the group consisting of: phenyl and phenyl substituted with one or three fluorine substituents;

and/or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 selected from:

3-{[(2S)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinamine; and

3-{[(2S)-2-amino-3-(2,3,4-trifluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinamine;

and/or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 that is:

3-{[(2S)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinamine;

and/or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a compound of claim 1, and/or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising the compound of claim 4, and/or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. 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 thereof, which process comprises bringing the compound of claim 1 and/or a pharmaceutically acceptable salt thereof into association with a pharmaceutically acceptable carrier.

8. 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 thereof.

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

10. 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 the compound of claim 4 and/or a pharmaceutically acceptable salt thereof.

11. The method of claim 10 wherein the mammal is a human.

12. The method according to claim 9 wherein said cancer is selected from: brain (gliomas), glioblastomas, leukemias, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone and thyroid.

13. The method according to claim 9 wherein said cancer is selected from: Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma and Erythroleukemia.

14. The method according to claim 9 wherein said cancer is selected from: malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma and follicular lymphoma.

15. The method according to claim 9 wherein said cancer is selected from: neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

16. A method of treating or lessening the severity of a pre-cancerous syndrome in a mammal, wherein the pre-cancerous syndrome is selected from: myelodysplastic syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithleial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis (especially viral induced hepatitis) which can progress to cancer.

17 The method of claim 16 wherein the mammal is a human.

18. Use of a compound of claim 1 and/or a pharmaceutically acceptable salt 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.

19. 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 thereof.

20. 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 thereof; and

b) at least one anti-neoplastic agent.

21. The method claim 20, 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.

22. The method of claim 20, wherein the at least one anti-neoplastic agent is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

23. The method of claim 20, wherein the at least one anti-neoplastic agent is a diterpenoid.

24. The method of claim 20, wherein the at least one anti-neoplastic agent is a vinca alkaloid.

25. The method of claim 20, wherein the at least one anti-neoplastic agent is a platinum coordination complex.

26. The method of claim 20, wherein the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

27 The method of claim 20, wherein the at least one anti-neoplastic agent is paclitaxel.

28. The method of claim 20, wherein the at least one anti-neoplastic agent is carboplatin.

29. The method of claim 20, wherein the at least one anti-neoplastic agent is vinorelbine.

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

31. The method of claim 30, 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.

32. The method of claim 30, 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.

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

34. The method of claim 33, wherein the signal transduction pathway inhibitor is an inhibitor of c-src.

35. The method of claim 30, wherein the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

36. The method of claim 30, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

37. The method of claim 20, wherein the at least one anti-neoplastic agent is a cell cycle signaling inhibitor.

38. The method of claim 37, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.

39. A pharmaceutical combination as claimed in claim 20 for use in therapy.

40. The use of a pharmaceutical combination as claimed in claim 20 for the preparation of a medicament useful in the treatment of cancer.

41. 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 3-{[(2S)-2-amino-3-(3-fluorophenyl)propyl]oxy}-6-(2-methyl-3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinamine; and/or a pharmaceutically acceptable salt thereof.

42. The method of claim 20 wherein the anti-neoplastic agent is N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/74371

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90; A61K 31/415, 31/519 (2008.04)
USPC - 514/264.1, 406
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/264.1, 406

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/403 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); GoogleScholar
Search Akt, protein kinase B, apoptosis, pyridine substituted compounds, anti-apoptotic, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/085227 A1 (YAMASHITA et al.) 15 September 2005 (15.09.2005) Abstract; pg 7, ln 20-25; pg 54, compound 186, pg 58, ln 10-15; pg 59, ln 29-35; pg 61, ln 25-30; pg 62, ln 19-23; pg 68, ln 10-20, pg 74, ln 25-30; pg 75, ln 5-10; pg 159, col 10-20; pg 168, ln 30-35	1-15 and 18-42
Y	US 2004/0106540 A1 (BARNETT et al.) 3 June 2004 (03.06.2004) para [0126], [0142]-[0144]	1-15 and 18-42
Y	US 2006/0258657 A1 (BRUNCKO et al.) 16 November 2006 (16.11.2006) para [0876]	42

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 2008 (17.11.2008)	09 DEC 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/74371

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-17
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 16-17 are unsearchable as the method does not recite any postive steps as per PCT Rule 6.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.