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(54) Title: CRYSTALLINE *N*-{(1-S)-2-AMINO-1-[(3-FLUOROPHENYL)METHYL]ETHYL}-5-CHLORO-4-(4-CHLORO-1-METHYL-1*H*-PYRAZOL-5-YL)-2-THIOPHENECARBOXAMIDE HYDROCHLORIDE

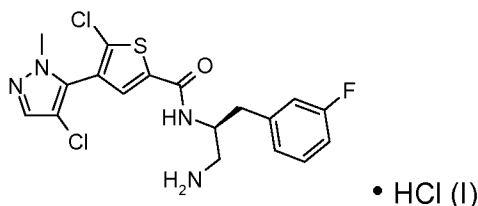
(57) Abstract: An improved AKT inhibiting compound, crystalline *N*-{(1 S)-2-amino-1-[(3- fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1 -methyl-1 *H*-pyrazol-5-yl)-2- thiophenecarboxamide hydrochloride.



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CRYSTALLINE *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride

This invention relates to an improved protein kinase B (hereinafter PKB/Akt, PKB or AKT) inhibiting compound, the hydrochloride salt of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide in crystalline form. The compound is represented by Structure I:



The compound of this invention is useful as an inhibitor of AKT activity, and in the treatment of cancer and arthritis.

Brief Description of the Drawings

Figure – 1 Figure 1 depicts a Powder X-Ray Diffraction (PXRD) pattern of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide in crystalline form.

Figure – 2 Figure 2 depicts a Powder X-Ray Diffraction (PXRD) pattern of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide in crystalline form.

Figure – 3 Figure 3 depicts a Powder X-Ray Diffraction (PXRD) pattern of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide in amorphous form.

Detailed Description of the Invention

N-{(1*S*)-2-Amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide is a compound which is disclosed and claimed, along with pharmaceutically acceptable salts thereof, as being useful as an inhibitor of AKT activity, particularly in the treatment of cancer and arthritis, in International

Application No. PCT/US08/053269, having an International filing date of February 7, 2008; International Publication Number WO 08/098104 and an International Publication date of August 14, 2008 (compound of Example 96). The entire disclosure of which is hereby incorporated by reference. International Application No. PCT/US08/053269
5 discloses the preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride. However the hydrochloride form prepared by the process in Example 96 of International Application No. PCT/US08/053269 is amorphous.

It has now been found that the hydrochloride salt of *N*-{(1*S*)-2-amino-1-[(3-
10 fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide can be prepared in crystalline form and that the crystalline form has numerous advantages over the free acid and other salt forms, including the amorphous hydrochloride form. The crystalline form of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-
15 thiophenecarboxamide hydrochloride is more readily formulated into pharmaceutical dosage forms, particularly tablets and has improved chemical stability. The crystalline form is a non-hygroscopic anhydrous form, and exhibits good solubility in bio-relevant media. The amorphous form is hygroscopic.

While the free compound is highly useful as an inhibitor of AKT activity,
20 particularly in treating cancer and arthritis, the crystalline form of the hydrochloride salt of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide has added advantages.

The compound of this invention, *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride in
25 crystalline form (hereinafter - "Active Ingredient" or "Compound A"), is useful as an inhibitor of AKT activity, particularly in the treatment of cancer and arthritis. The Active Ingredient can be administered in a conventional dosage form prepared by combining the Active Ingredient with a conventional pharmaceutically acceptable carrier or diluent according to techniques readily known to those of skill in the art, such as those described
30 in International Application No. PCT/US08/053269.

Suitably, the present invention includes within its scope pharmaceutical compositions comprising *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride in crystalline
35 form, as the Active Ingredient, in association with a pharmaceutically acceptable carrier or diluent. Compound A of this invention can be administered by oral, parenteral,

intradermal or topical routes of administration. The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intranasal, intrarectal, intravaginal and intraperitoneal administration. Oral administration is generally preferred. Compound A can be formulated in dosage forms appropriate for each route of administration

5 including capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is generally admixed with at least one inert diluent. The oral dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents, glidants and antioxidants. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills
10 can additionally be prepared for a sustained release.

Preparations according to this invention for parenteral administration include sterile aqueous solutions although nonaqueous suspensions of emulsions can be employed. Such dosage forms may also contain adjuvants such as preserving, wetting, osmotic, buffering, emulsifying and dispersing agents. They may be sterilized by, for
15 example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, irradiating the compositions or by heating the compositions.

Doses of the presently invented Active Ingredient in a pharmaceutical dosage unit as described above will be an efficacious quantity preferably selected from the range of 0.001 - 100 mg/kg of total body weight, preferably 0.001 - 50 mg/kg. When treating a
20 human patient in need of AKT inhibition, in need of treatment for cancer, in need of treatment for arthritis, the selected dose is preferably administered from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of Active Ingredient, most
25 preferably from 0.5 to 1,000 mg of Active Ingredient. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient. The above dosages relate to the preferred amount of the Active Ingredient expressed as the free acid.

It will be recognized by one of skill in the art that the optimal quantity and spacing
30 of individual dosages of the Active Ingredient will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the Active Ingredient given per day for a defined

number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Generally speaking, the compound of this invention is prepared by dissolving the free base, *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, in an appropriate organic solvent, such as methyl t-butyl ether (MTBE), then adding to this solution HCl, for example, 4M HCl in dioxane, with heating, for example to 42° C for 4 hours. The solution is allowed to cool and the compound of this invention is filtered off and dried, for example, dried in vacuo or air dried at an elevated temperature.

Organic solvents are available from the Aldrich Chemical Company, Milwaukee, Wisconsin.

Because the pharmaceutically active compound of the present invention is active as an inhibitor of AKT it exhibits therapeutic utility in treating cancer and arthritis.

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

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, 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, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

As disclosed in PCT/US2008/053269, the compound of this invention prepared as in PCT/US2008/053269 was tested for activity generally according to the AKT enzyme assays disclosed in PCT/US2008/053269, and in at least one experimental run exhibited

a pIC50 value: equal to 9.0 against full length AKT1; equal to 8.0 against full length AKT2; and equal to 8.8 against full length AKT3.

By the term "treating" and derivatives thereof as used herein, is meant therapeutic therapy. Prophylactic therapy is appropriate, for example, when a subject is considered
5 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
10 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.

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of Compound A 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
20 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
25 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
30 & 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
35 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 Compound A are chemotherapeutic agents.

10 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.

15 Diterpenoids, which are derived from natural sources, are phase specific anti - cancer agents that operate at the G₂/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β -tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

20 Paclitaxel, 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. It was first isolated in 1971 by Wani et al. J. Am. Chem. Soc., 93:2325.
25 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
30 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,
35 64:583, 1991; McGuire et al., Ann. Intern. Med., 111:273,1989) and for the treatment of

breast cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797, 1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

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

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

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

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincalurekoblamine [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, anthracyclins such as daunorubicin and doxorubicin; and bleomycins.

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

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 G₂ phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-ethylidene- β -D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single 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-O-(R)-thenylidene- β -D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in 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, mercaptopurine, thioguanine, and gemcitabine.

5 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
10 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
15 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,
20 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
25 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
30 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
35 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-pteridiny) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dihydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

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

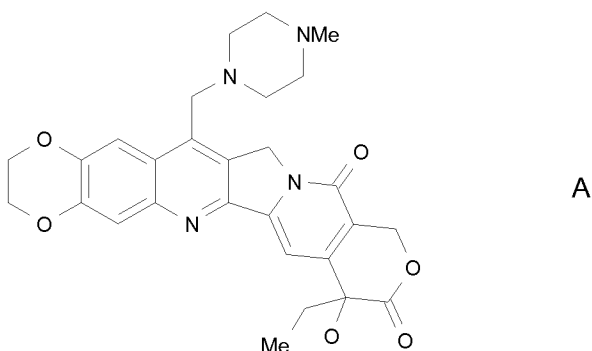
Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

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

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is

commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of single 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:



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

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrozole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5 α -reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign

prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, idoxifene, 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
5 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
10 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.

15 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.
20 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
25 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)
30 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
35 function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000)

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

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases 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-lacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

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

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

5 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
10 inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), *Journal of Biomedical Science*. 7(4) 292-8; Ashby, M.N. (1998), *Current Opinion in Lipidology*. 9 (2) 99 – 102; and *BioChim. Biophys. Acta*, (1989) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway
15 inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, *Monoclonal Antibody Therapy for Solid Tumors*, *Cancer Treat. Rev.*, (2000), 26(4), 269-286); Herceptin® erbB2 antibody (see *Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases*, *Breast Cancer Res.*,
20 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
25 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
30 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),
35 *Oncogene* 19: 3460-3469).

Agents used in immunotherapeutic regimens may also be useful in the present invention. 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
5 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
10 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
15 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
20 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
25 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 of Compound A and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum
30 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.

Compound A of this invention is useful as an inhibitor of AKT, in the treatment of
35 cancer and arthritis in mammals, particularly humans, in need thereof.

The method of this invention of treating cancer and arthritis in mammals, including humans, comprises administering to a subject in need of such treatment a therapeutically effective amount of Compound A of the present invention.

The invention also provides for the use of Compound A in the manufacture of a medicament for use in therapy.

The invention also provides for the use of Compound A in the manufacture of a medicament for use as an AKT inhibitor.

The invention also provides for the use of Compound A in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of Compound A in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises Compound A and a pharmaceutically acceptable carrier.

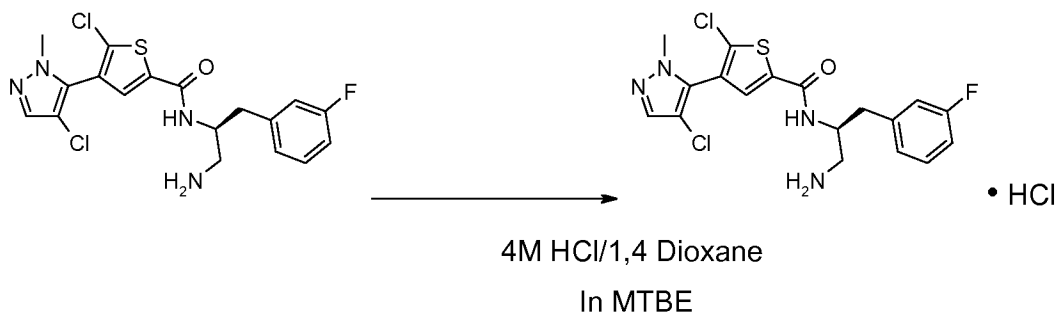
The invention also provides for a pharmaceutical composition for use in the treatment of arthritis which comprises Compound A and a pharmaceutically acceptable carrier.

The following examples further illustrate the present invention. The examples are not intended to limit the scope of the invention as defined hereinabove and as claimed below.

EXAMPLE 1

Preparation of: Crystalline

N-{(1*S*)-2-Amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride



Amorphous *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide free base is prepared as described in International Application No. PCT/US08/053269. 1 mL of methyl t-butyl ether (MTBE) is

added to a vial containing 50.8 mg of amorphous *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide free base. Most of the solid dissolved. After addition of the HCl acid (1 eq., 29.7mL of 4M HCl in 1,4-dioxane) to the reaction mixture, a white solid
5 material crashed out quickly at room temperature. An aliquot of the reaction mixture was analyzed by polarized light microscopy (PLM) and the solid was found to be amorphous. The slurry was then heated to 40° C with magnetic stirring to dissolve most of the solid material. The thin slurry was stirred at 40° C overnight, and then cooled from 40° C to 25° C. A thick white slurry formed. An aliquot of the reaction mixture was analyzed by
10 polarized light microscopy (PLM) and the solid was found to be crystalline. The white solid was collected by vacuum filtration, and then dried at 50° C overnight. The product was determined be a crystalline solid by the Powder X-Ray Diffraction (PXRD) pattern depicted in Figure 1.

15 **Instrument:** Rigaku Miniflex II, Serial DD02652

Key Operating Parameters:

Method Normal Run

The sample is scanned using the following parameters:

20 Scan range: 2-40 degrees two-theta

Generator power: 30kV, 15mA

Radiation Source: Cu KAlpha

Scan mode: FT

Count time: 1.0 seconds

25 Step width: 0.020 degrees two-theta per step

Scan axis: 2theta/theta

Incident Beam optics: $\pm 2.5^\circ$ divergence angle soller slit, 1.25 degree divergent slit, 0.3mm

RecSlit, 1.25 degrees anti-scatter slit

Diffacted Beam optics: fixed slits (MiniFlex II), $\pm 2.5^\circ$ soller slits

30 Detector Type: Rigaku MiniFlex II SC (Scintillator Counter)

The sample is packed into a zero background sample holder (100 μ m indent) and gently flattened using a glass slide.

35

EXAMPLE 2

Preparation of: Crystalline

N-{(1*S*)-2-Amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride

5

5 mL of MTBE was added to 213.9 mg of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide amorphous free-base (0.500 mMol.). The mixture was heated to 40° C with magnetic stirring for 1 hour. A solution of 4M HCl in 1,4-dioxane (1 eq; 125.1 uL) was added in four equal portions. After addition of the first portion (0.25 eq), the mixture was heated to 42° C and 1 mL of acetonitrile was added to dissolve all of the solid material. After the remainder of the HCl solution was added, some solid material appeared. The slurry was stirred at 42° C for 4 hours, then was cooled slowly to 22° C overnight with 90 minute holds at 35° C, 30° C, and 25° C. The white solid material was filtered and dried at 50° C under vacuum with a slow nitrogen bleed overnight. The yield was 73.6% (0.3685 mmol; 170.90 mg) of the HCl salt. The solid was found to be 1:1 stoichiometric HCl salt by ion chromatography, and to be crystalline by the Powder X-Ray Diffraction (PXRD) pattern depicted in Figure 2 and as characterized by diffraction peaks below, and to have a melting point of 211° C.

20

PXRD peaks (values given in degrees two-theta with d-spacing in parenthesis):

	7.2(12.20)	14.4(6.16)	17.9(4.94)	18.5(4.79)	20.8(4.26)
	21.5(4.12)	22.4(3.96)	22.9(3.88)	23.7(3.75)	24.5(3.63)
	24.7(3.61)	25.1(4.12)	25.7(3.46)	27.3(3.26)	28.2(3.16)
25	28.8(3.10)	30.4(2.94)	32.4(2.76)	32.7(2.73)	35.2(2.55)
	36.1(2.48)	40.0(2.25)	41.3(2.18)	41.7(2.16)	

Instrument: PANalytical X'Pert-Pro MPD with Johansson K α 1 monochromator, using X'Celerator detector

30

Key Operating Parameters:

Radiation: Cu ($K\alpha_1$), 1.540598 angstroms (monochromatic)

Detector: X'Celerator

Tension: 45 kV

5 Current: 40 mA

Start angle: $2.0^\circ 2\theta$

End angle: $52.0^\circ 2\theta$

Step size: 0.02°

Time/step: 40.0 sec

10 Scan speed: $0.05^\circ/\text{sec}$

Incident beam: 2° fixed anti-scatter slit, and programmable divergence slit

Diffacted beam: 0.02 rad soller slit, and programmable anti-scatter slit

Samples prepared on silicon zero background sample holder.

15

EXAMPLE 3

Preparation of: Amorphous

N-{(1*S*)-2-Amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride

20

The hydrochloride salt of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide prepared generally as described in Example 96 of International Application No. PCT/US2008/053269, having an International Filing date of February 7, 2008, and having International Publication

25 Number WO/2008/098104 and an International Publication Date of August 14, 2008,

which generally states that the free base compound, *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, is treated with 4M HCl in dioxane and after 5 min, the solution is concentrated and dried under vacuum to afford *N*-{(1*S*)-2-amino-1-[(3-

30 fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride, yielded an amorphous solid as indicated by the Powder X-Ray Diffraction (PXRD) pattern depicted in Figure 3.

Instrument: Rigaku Miniflex II, Serial DD02652

Key Operating Parameters:

Method Normal Run

5 The sample is scanned using the following parameters:

Scan range: 2-40 degrees two-theta

Generator power: 30kV, 15mA

Radiation Source: Cu KAlpha

Scan mode: FT

10 Count time: 1.0 seconds

Step width: 0.020 degrees two-theta per step

Scan axis: 2theta/theta

Incident Beam optics: $\pm 2.5^\circ$ divergence angle soller slit, 1.25 degree divergent slit, 0.3mm

RecSlit, 1.25 degrees anti-scatter slit

15 Diffracted Beam optics: fixed slits (MiniFlex II), $\pm 2.5^\circ$ soller slits

Detector Type: Rigaku MiniFlex II SC (Scintillator Counter)

The sample is packed into a glass sample holder and gently flattened using a glass slide.

20

EXAMPLE 4

Tablet Composition

Lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and crystalline *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are blended in the proportions shown in Table 1 below. The blend is then compressed into tablets.

Table 1

INGREDIENT	mg.
crystalline <i>N</i> -{(1 <i>S</i>)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1 <i>H</i> -pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride	8.45
microcrystalline cellulose	112
lactose	70
sodium starch glycolate	8
magnesium stearate	2

EXAMPLE 5

Injectable Parenteral Composition

An injectable form for administering the active ingredient is produced by stirring 5.0 mg. of crystalline *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride in 1.0 ml. of normal saline.

EXAMPLE 6

Hygroscopicity

10

Crystalline

Crystalline *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride made generally according to Example 1, and confirmed to be crystalline by PXRD, was tested using a VTI instrument SGA 100 using the following method.

15

Sample Preparation:

Solvent:	Water		
Drying Temp (°C):	No drying		
Experiment Temp (°C):	25		
20 Max Equilibrium Time (min)	240		
Equilibrium Criteria (wt %):	0.0025	in	10 min
Data Logging Interval (min):	2	or	0.01 wt %

25

There were 24 Relative Humidity steps used. The Relative Humidity at each step is as follows.

1 – 40; 2 – 50; 3 – 60; 4 – 70; 5 – 80; 6 – 90; 7 – 80; 8 – 70; 9 – 60; 10 – 50;
 11 – 40; 12 – 30; 13 – 20; 14 – 10; 15 – 5; 16 – 10; 17 – 20; 18 – 30; 19 – 40;
 20 – 50; 21 – 60; 22 – 70; 23 – 80; and 24 – 90.

30

The weight increase of the compound was less than 1% w/w moisture, indicating the compound has a low level of hygroscopicity.

Amorphous

In a separate experiment on a different day, amorphous *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride (confirmed to be amorphous by PXRD), was tested
5 using a VTI instrument SGA 100 using the following method.

Sample Preparation:

10	Solvent:	Water		
	Drying Temp (°C):	60		
	Heating Rate (°C/min):	1		
	Max Drying Time (min):	120		
	Experiment Temp (°C):	25		
	Max Equilibrium Time (min)	300		
	Equilibrium Criteria (wt %):	0.0025	in	10 min
	Data Logging Interval (min):	2	or	0.01 wt %

15

There were 19 Relative Humidity steps used. The Relative Humidity at each step is as follows.

1 – 0; 2 – 10; 3 – 20; 4 – 30; 5 – 40; 6 – 50; 7 – 60; 8 – 70; 9 – 80; 10 – 90;
11 – 80; 12 – 70; 13 – 60; 14 – 50; 15 – 40; 16 – 30; 17 – 20; 18 – 10; and 19 – 0.

20

The weight increase of the compound was more than 18% w/w moisture, indicating the compound has a high level of hygroscopicity.

25

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. *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride in crystalline form.

5

2. A pharmaceutical composition comprising *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride in crystalline form and a pharmaceutically acceptable carrier or diluent.

10

3. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier and an effective amount of a compound of claim 1, which process comprises bringing the compound of claim 1 into association with a pharmaceutically acceptable carrier.

15

4. A method of treating or lessening the severity of a disease or condition selected from: cancer and arthritis, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of claim 1.

20

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

6. The method according to claim 5 wherein said cancer is selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

25

7. Use of a compound of claim 1 in the manufacture of a medicament for use in treating or lessening the severity of a disease or condition selected from cancer and arthritis.

30

8. The method of inhibiting Akt activity in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of claim 1.

35

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

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

- 5 a) a compound of claim 1; and
 b) at least one anti-neoplastic agent.

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

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

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

20

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

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

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

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

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

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

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

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

10

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

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

15

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

20

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

26. The method of claim 20, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

25

27. The method of claim 10, wherein the at least one anti-neoplastic agent is a cell cycle signaling inhibitor.

30

28. The method of claim 27, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.

29. A pharmaceutical combination as claimed in claim 10 for use in therapy.

35

30. The use of a pharmaceutical combination as claimed in claim 10 for the preparation of a medicament useful in the treatment of cancer.

31. The method according to claim 5 wherein said cancer is selected from:
5 brain (gliomas), glioblastomas, 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, thyroid,
10 Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic
15 leukemia, promyelocytic leukemia, Erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer,
20 salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

32. A method of treating or lessening the severity of cancer in a mammal in
25 need thereof, which comprises administering to such mammal a therapeutically effective amount of: *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride in crystalline form.

33. The method of claim 32 wherein the mammal is a human.
30

34. The method of claim 5 wherein the compound is administered orally.

35. The method of claim 5 wherein the compound is administered parenterally.

36. A method of treating or lessening the severity of cancer in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a composition of claim 2

5 37. The method of claim 36 wherein the mammal is a human.

38. The method of claim 37 wherein the compound is administered orally.

10 39. The method of claim 37 wherein the compound is administered parenterally.

40. The method according to claim 37 wherein said cancer is selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's
15 sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute
20 myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

25 malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, 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, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular
30 cancer.

41. Crystalline *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride of claim 1
35 having characteristic diffraction peaks at $14.4^{\circ} \pm 0.3^{\circ}$ and $32.4^{\circ} \pm 0.3^{\circ}$ in an Powder X-Ray Diffractogram using Cu K α radiation.

42. Crystalline *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride having the characteristic diffraction peaks recited in claim 41 and having characteristic diffraction
5 peaks at $25.1^{\circ} \pm 0.3^{\circ}$ and $25.7^{\circ} \pm 0.3^{\circ}$ in the Powder X-Ray Diffractogram using Cu K α radiation.

43. Crystalline *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride having the
10 characteristic diffraction peaks recited in claim 42 and having characteristic diffraction peaks at $21.5^{\circ} \pm 0.3^{\circ}$ and $20.8^{\circ} \pm 0.3^{\circ}$ in the Powder X-Ray Diffractogram using Cu K α radiation.

44. A pharmaceutical composition comprising crystalline *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride having the characteristic diffraction peaks recited in
15 claim 41 and a pharmaceutically acceptable carrier or diluent.

45. A method of treating or lessening the severity of cancer in a mammal in
20 need thereof, which comprises administering to such mammal a therapeutically effective amount of a composition of claim 44

46. The method of claim 45 wherein the mammal is a human.

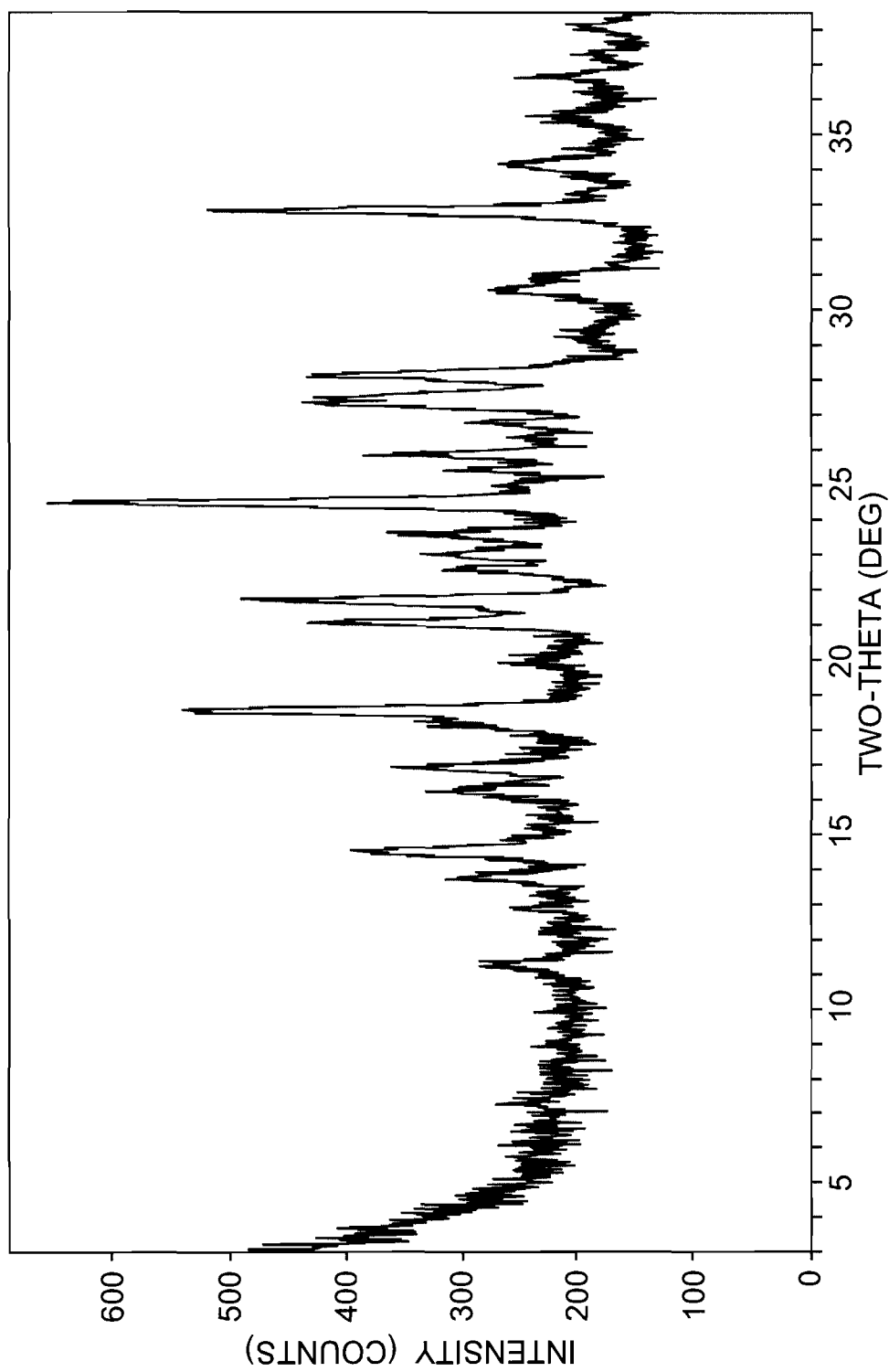
47. The method of claim 46 wherein the compound is administered orally.

48. The method of claim 46 wherein the compound is administered
parenterally.

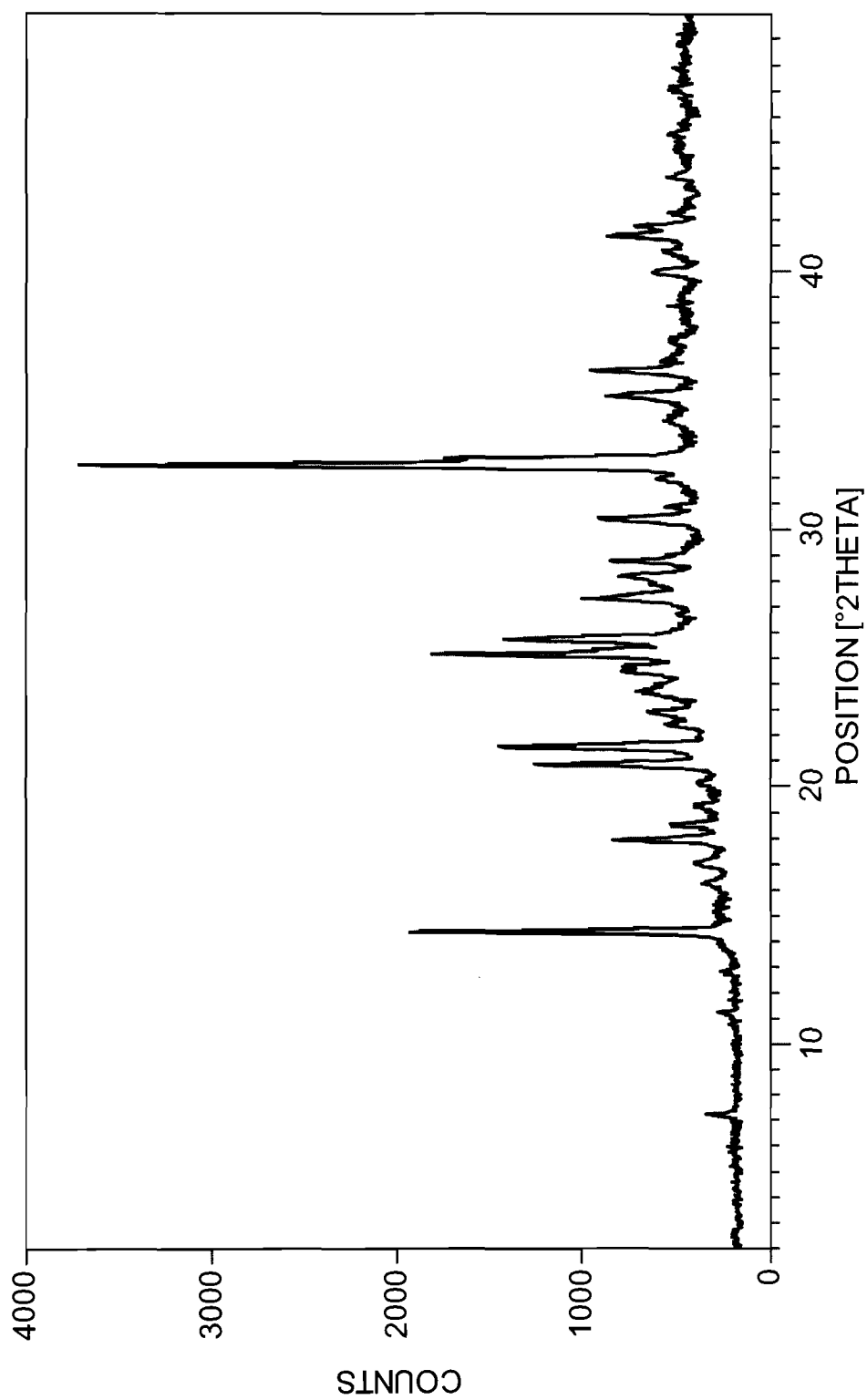
49. The method according to claim 46 wherein said cancer is selected from:
30 brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma,
35 giant cell tumor of bone, thyroid,

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,
5 Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,
malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,
neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer,
10 cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

1/3

**FIG. 1**

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**FIG. 2**

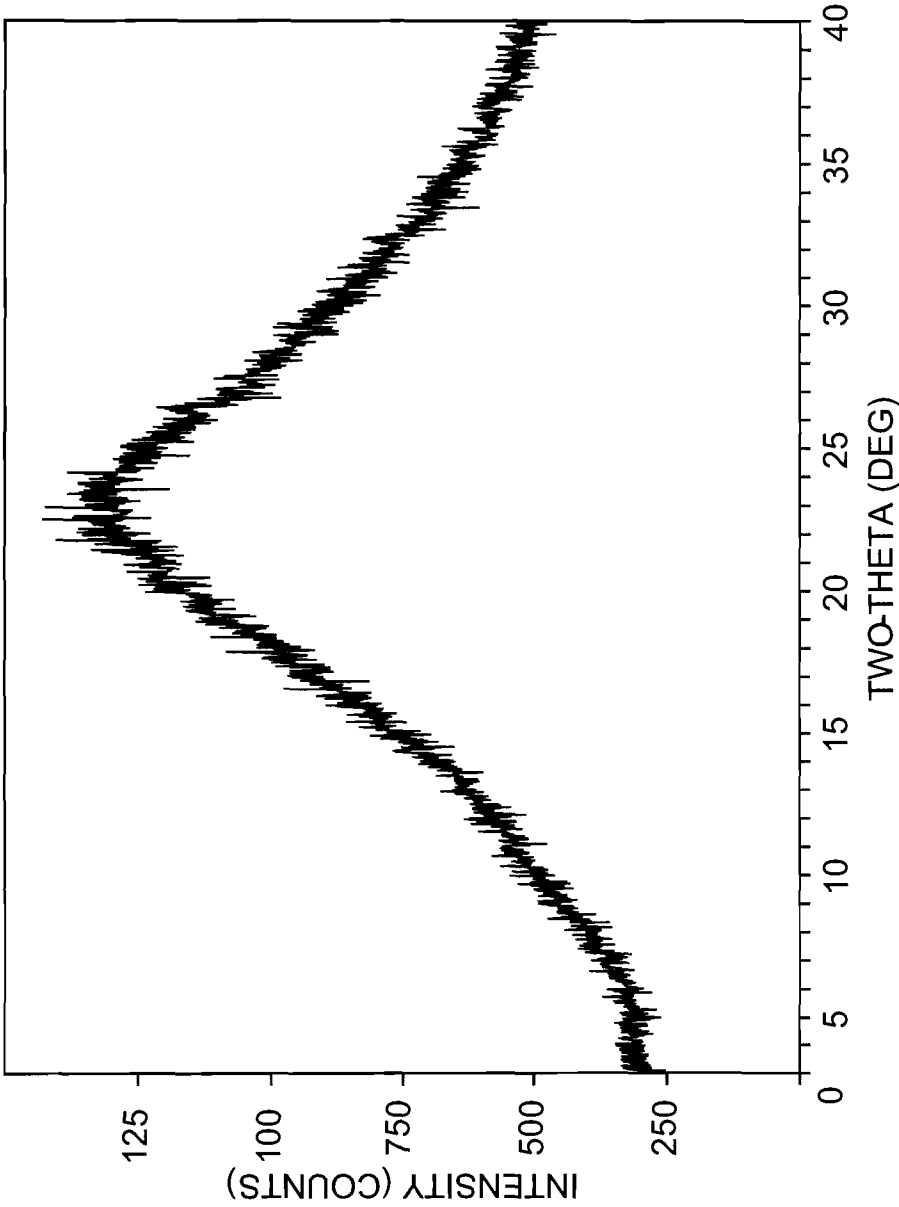


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/22323

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/381 (2010.01)

USPC - 549/72

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)

IPC(8): A61K 31/381 (2010.01)

USPC - 549/72

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC - 549/1, 29, 30; 514/183, 359, 366, 403, 405, 430, 438, 448, 706, 740, 741, 747; 568/77; IPC(8) - A61K 31/33, 31/38, 31/41, 31/025, 31/381, 31/415; C07D 333/02 (2010.01); Term search-- see search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 USPTO PubWEST(USPT, PGPB, EPAB, JPAB); Dialogweb (344, 347, 348, 349, 371, 652, 654, 345, 351, 315, 35, 440, 155); USPTO online search; Google Scholar; Search terms: \$thiophenecarboxamide, cancer, arthritis, fluorophenyl\$, \$diazole, pyrazole, pyrazolyl, pyrazol-5-yl, 3-fluorophenyl\$, 3-fluorobenzyl\$, 3-fluorophenylalkyl\$, inhibitor, kinase, fluoro

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7,074,801 B1 (YOSHIDA, et al.) 11 July 2006 (11.07.2006), col 1, ln 14-16; col 2, ln 14-19; col 2, ln 27-33; col 510, ln 18-32, Example 447; col 738, ln 25-30, Example 869; col 794, ln 10-28, Example 989	1-49
A	US 2006/0014816 A1 (ARNOLD, et al.) 19 January 2006 (19.01.2006), para [0002]-[0004], [0362], Example 144	1-49
A	US 2006/0074119 A1 (ANDREWS, et al.) 06 April 2006 (06.04.2006), para [0001]-[0004], [0469], Example 15	1-49
A	US 7,157,456 B2 (STRAUB, et al.) 02 January 2007 (02.01.2007), col 2, ln 33-50; col 21, ln 25-35	1-49
A	US 7,034,049 B1 (PEVARELLO, et al.) 25 April 2006 (25.04.2006), col 2, ln 13-33; col 6, ln 45-48; col 10, ln 47-48, compound 142	1-49
A	US 6,982,279 B2 (PEUKERT, et al.) 03 January 2006 (03.01.2006), col 9, ln 20-26; col 19, ln 12-16, compound 9	1-49
A	US 5,369,124 A (ELBE, et al.) 29 November 1994 (29.11.1994), col 2, ln 29-31; col 9, ln 12-15, Example 2	1-49
A	US 2008/0027044 A1 (LEWIS, et al.) 31 January 2008 (31.01.2008), para [0016], Claim 24, Compound 18	1-49

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


* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

15 March 2010 (15.03.2010)

Date of mailing of the international search report

09 APR 2010

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/22323

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/0171741 A1 (WROBLESKI, et al.) 17 July 2008 (17.07.2008), para [0007], [0368], Table 7, Example 174	1-49