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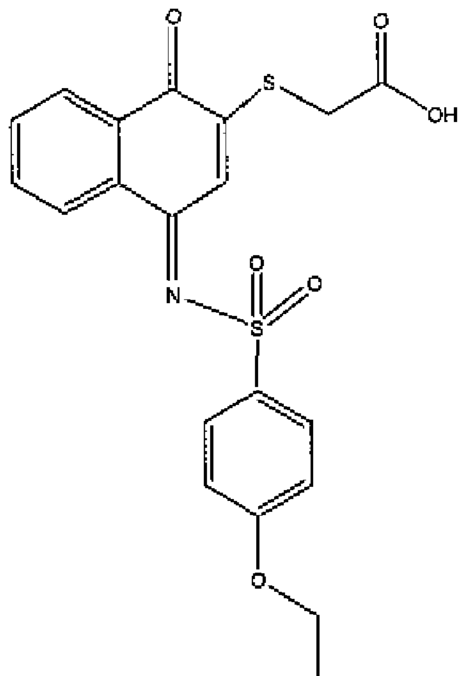
(54) Title: METHOD OF TREATING OR PREVENTING CANCER



(57) Abstract: Disclosed is a method for inhibiting Akt, activating AMPK, inhibiting mTOR, treating or preventing development of cancer, and/or preventing progression of premalignant lesions to cancer in an animal comprising administering to the animal an effective amount of a compound as described herein, for example, NSC 743411, whose formula is set forth below. The method involves the use of these compounds as single agents or in combination with conventional chemotherapy, biological therapy, or radiation therapy. The invention further provides novel compounds and pharmaceutical compositions for use in treating or preventing development of cancer or preventing the progression of premalignant lesions into cancer. Also disclosed is a method of inhibiting CSF1R.

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METHOD OF TREATING OR PREVENTING CANCER

CROSS-REFERENCE TO A RELATED APPLICATION

[0001] The present application claims the benefit of U.S. provisional patent application No. 61/226,328, filed July 17, 2009, the disclosure of which is incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Cancer is a major world-wide health problem. Those afflicted with cancer suffer physically and emotionally and, unless treated in a timely manner, die an early death. There is also a tremendous burden on the families and friends of those afflicted as well as on society at large. Although many drugs are in use for cancer treatment, there is a desire for additional cancer treatment agents. In addition, there is a desire for a method to prevent cancer, delay or slow down its onset and/or progression, or to prevent the progression of precancerous lesions into cancer.

[0003] Akt is at the nexus of many signaling pathways and is thought to be an important target for therapeutic intervention in cancer. Activation of Akt occurs through ligand binding to growth factor receptors, activation of various oncogenes such as Ras, Egfr and Her2 or inactivation of tumor suppressor genes such as PTEN. Akt activation has been detected in a high percentage of multiple tumor types, as well as many types of premalignant lesions. Thus, enhanced activation of Akt likely contributes to the pathogenesis and/or maintenance of a wide variety of human malignancies, which is supported by the poor clinical outcomes associated with Akt activation in many of these tumors.

[0004] Akt is a serine/threonine kinase with diverse targets involved in protein synthesis, cell cycle progression and resistance to apoptosis. *In vitro* as well as clinical studies have suggested that Akt may be an important target for cancer therapy. Akt is constitutively active in NSCLC cell lines and promotes resistance to chemotherapy drugs and radiation *in vitro*. Activation and overexpression of Akt are often associated with resistance to chemotherapy or radiotherapy in patients as well. Phosphorylation of Akt at S473, a marker of Akt activation, has been correlated with poor clinical outcomes in many tumor types, including lung, melanoma, breast, prostate, endometrial, gastric, pancreatic, and brain cancers, as well as acute myelogenous leukemia. Reversal of drug resistance

coupled with Akt inhibition has been demonstrated in both cell-based studies and animal models by PI3K inhibitors and by PTEN overexpression in PTEN-null cells. Dominant-negative mutants of Akt were also shown to enhance cytotoxicity by chemotherapeutic agents suggesting an important role of Akt in drug resistance. Furthermore, inhibition of receptor tyrosine kinases, such as epidermal growth factor receptor, sensitizes cells to chemotherapy or radiotherapy through downregulation of the PI3K–Akt pathway.

[0005] Thus, there is a desire for providing a method for treating or preventing the development of cancer or preventing the progression of precancerous lesions into cancer that employs an Akt inhibitor.

BRIEF SUMMARY OF THE INVENTION

[0006] The invention provides a method for inhibiting mTOR, inhibiting Akt, activating AMPK, treating or preventing development of cancer, and/or preventing progression of premalignant lesions to cancer in an animal comprising administering to the animal an effective amount of a compound as described herein in greater detail. The method involves the use of these compounds as single agents or in combination with conventional cancer therapy such as chemotherapy, biological therapy, or radiation. The invention further provides novel compounds and pharmaceutical compositions for use in treating or preventing development of cancer or preventing the progression of premalignant lesions into cancer. The invention also provides a method of inhibiting CSF1R. Advantageously, one or more compounds of the invention have the ability to simultaneously inhibit Akt and activate AMPK, providing profound inhibition of mTOR and/or an anti-cancer effect.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] Fig. 1 depicts dose-dependent regulation of Akt/mTOR signaling by NSC743411. Non-small cell lung cancer cells (H1703, A549, and H157) were cultured in RPMI 5% FBS and treated with vehicle or increasing doses NSC743411 (N11) for 24 hours. Whole cell lysates were harvested and western blot analysis was performed.

[0008] Fig. 2 depicts time-dependent regulation of Akt/mTOR signaling by NSC743411. H1703 and H1155 (LKB1 wild-type NSCLC cells) were cultured in RPMI 5% FBS and treated with vehicle or N11 at indicated time points. Whole cell lysates were harvested and western blot analysis was performed.

[0009] Fig. 3 follows protein levels over time in the presence of DMSO or NSC743411. H157 and A549 (LKB1-deficient NSCLC cells) were cultured in RPMI 5% FBS and treated with vehicle or N11 at indicated time points. Whole cell lysates were harvested and western blot analysis was performed.

[0010] Fig. 4 depicts biomarker analysis of a NSC743411-treated H1703 xenograft. Xenograft tumors were harvested and frozen in liquid nitrogen. Samples were homogenized, resuspended in RIPA lysis buffer, and western blot analysis performed (15μg protein). The numbers 1071, 1074, 1069, 1078, 1073, 1072, 1077, and 1079 are mouse identification numbers.

[0011] Fig. 5 depicts the NCI 60 toxicity screen for NSC 743411, also known as N11, a compound in accordance with the invention, showing growth inhibition at micro-molar concentrations in a broad range of cell lines and cell killing at micro-molar concentrations in many cell lines. Fig. 5A depicts the screen for leukemia. Fig. 5B depicts the screen for colon cancer. Fig. 5C depicts the screen for ovarian cancer. Fig. 5D depicts the screen for non-small cell lung cancer. Fig. 5E depicts the screen for CNS cancer. Fig. 5F depicts the screen for renal cancer. Fig. 5G depicts the screen for breast cancer. Fig. 5H depicts the screen for melanoma. Fig. 5I depicts the screen for prostate cancer.

[0012] Fig. 6A depicts cell death induced by NSC 743411 in H1703 as assessed by propidium iodide uptake in accordance with an embodiment of the invention. Fig. 6B depicts minimal apoptosis is induced by NSC 743411 in H1703 as assessed by sub G1 cellular DNA content measured by flow cytometry. Fig. 6C depicts the morphology of H1703 cells with 24 h treatment of NSC 743411 in accordance with an embodiment of the invention.

[0013] Fig. 7 depicts *in vivo* inhibition of Akt phosphorylation, i.e., the levels of pS473 or pS6 normalized to total Akt + Standard deviation (p=0.31) in accordance with an embodiment of the invention. Western blots of crude WBC lysates were prepared 4 h after IP injection of 3 mice with 25 mg/kg NSC 743411 and 3 mice with vehicle only.

[0014] Fig. 8 depicts the fold change of tumor volume in mice after implantation of H1703 cells and injection of NSC 743411, in accordance with an embodiment of the invention. Data is reported as fold change in tumor volume relative to first day of dosing. Note that after Day 31, only odd-numbered days were monitored.

[0015] Fig. 9 depicts the percent change in body weight in mice after implantation of H1703 cells and injection of NSC 743411, in accordance with an embodiment of the invention. Data is reported as % change in body weight relative to first day of dosing. Note that after Day 31, only odd-numbered days were monitored.

[0016] Fig. 10 depicts the cell morphology change of A549 or H1703 cells by sulfonamide-2 in accordance with an embodiment of the invention. Fig. 10A depicts H1703 cells treated with DMSO only. Fig. 10B depicts the morphology of H1703 cells treated with sulfonamide-2. Fig. 10C depicts the morphology of A549 cells treated with DMSO only. Fig. 10D depicts the morphology of A549 cells treated with sulfonamide-2.

[0017] Fig. 11 depicts the GI50 values for cell growth inhibition by sulfonamide-2 as a function of compound concentration in μM, in accordance with an embodiment of the invention. Fig. 11A depicts growth inhibition of A549 cells as a function of concentration of sulfonamide-2. Fig. 11B depicts growth inhibition of H1703 cells as a function of concentration of sulfonamide-2.

[0018] Fig. 12 depicts that sulfonamide-2 arrests the G2/M phase of cell growth, in accordance with an embodiment of the invention. Fig. 12A depicts the percentage of H1703 cells in G2/M cell cycle phase as a function of time. Fig. 12B and Fig. 12C depict the number of H1703 cells vs. fluorescence in the presence of DMSO or sulfonamide-2, respectively. Fig. 12D depicts the percentage of survival of A549 cells as a function of time. Fig. 12E and Fig. 12F depict the number of A549 cells vs. fluorescence in the presence of DMSO or sulfonamide-2, respectively.

[0019] Fig. 13 depicts that sulfonamide-2 causes G2/M phase arrest and increases acetylated tubulin expression of A549 cells, in accordance with an embodiment of the invention. Fig. 13A depicts the morphology of A549 cells treated with DMSO only. Fig. 13B depicts the morphology of the cells treated with sulfonamide-2.

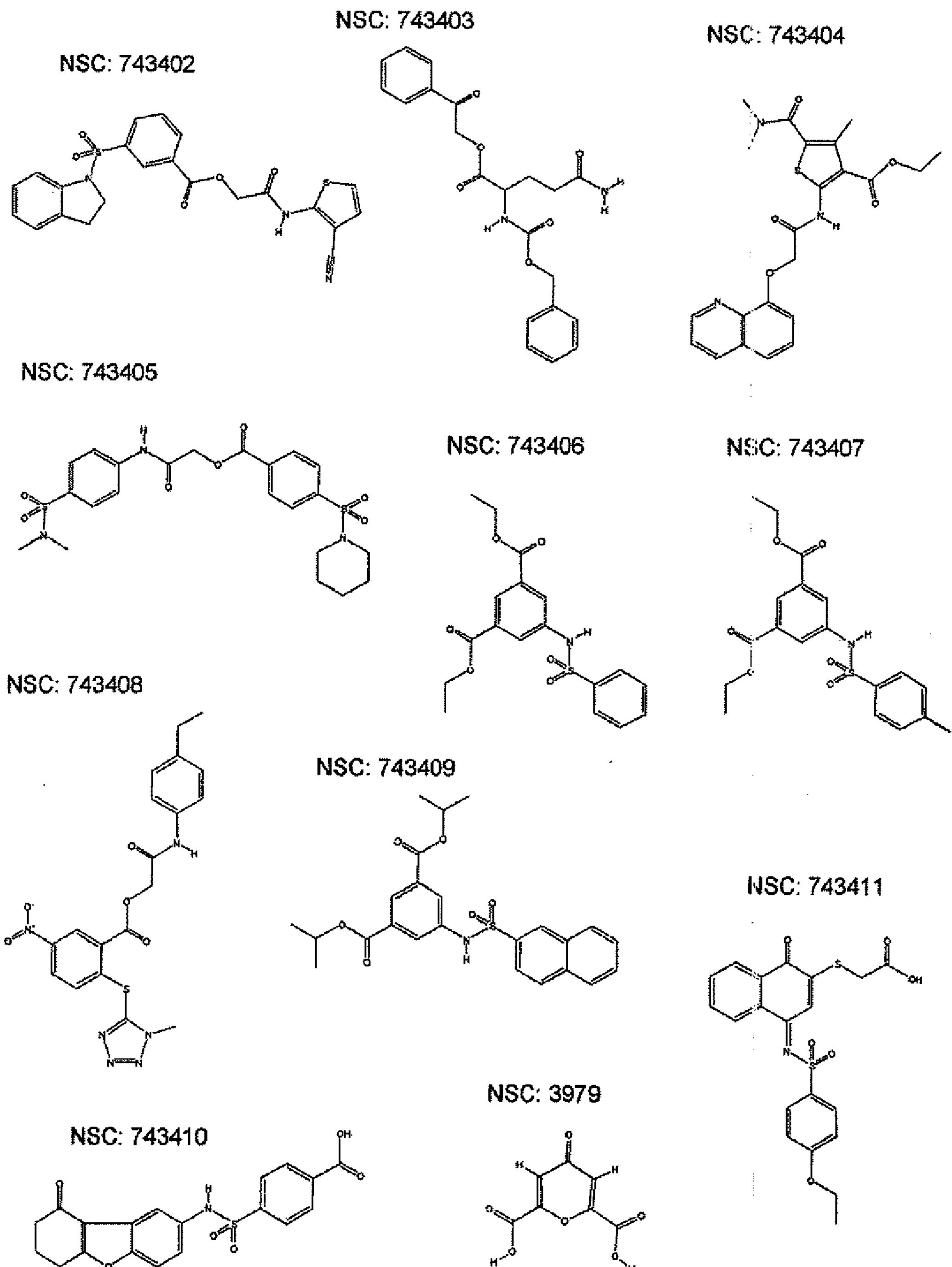
[0020] Fig. 14 depicts the percentage of viable cells of H1703 cells as a function of time. Cell death caused by sulfonamide-2 is shown by Trypan Blue staining, in accordance with an embodiment of the invention.

[0021] Fig. 15A depicts the number of viable H1703 cells treated with sulfonamide-2 on day 5 in full serum condition as a function of its fluorescence and Fig. 15B depicts the morphology of the cells, in accordance with an embodiment of the invention.

[0022] Fig. 16 depicts the percentage of nonapoptotic cell death of A549 cells with or without SiRNA, in accordance with an embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0023] In accordance with an embodiment, the invention provides a method for inhibiting mTOR comprising administering an effective amount of a compound having one of the following structures:



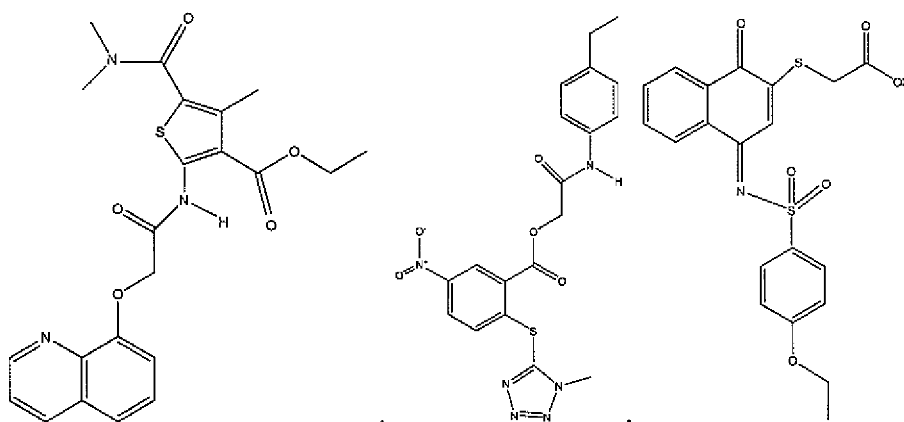
or a prodrug, salt, or solvate thereof.

[0024] In an embodiment, the present invention also provides a compound for inhibiting mTOR, wherein the compound has one of the above structures or a prodrug, salt, or solvate thereof.

[0025] The compounds above or prodrugs, salts, or solvates thereof inhibit the activation of Akt, particularly Akt1 in certain cancer cell types. In an embodiment, the

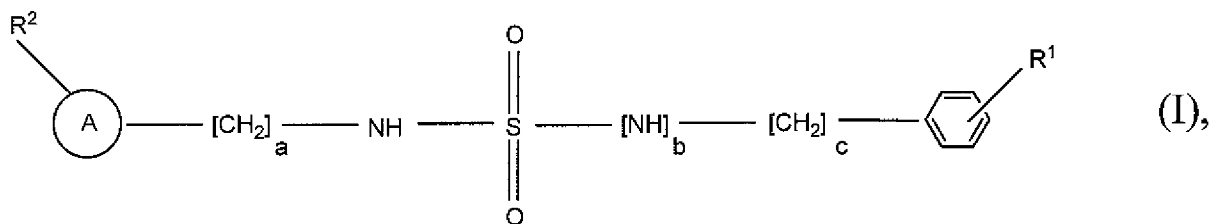
compounds inhibit the binding of Akt's pleckstrin homology (PH) domain to a phosphoinositide. In another embodiment, the compounds above activate AMP-activated protein kinase (AMPK).

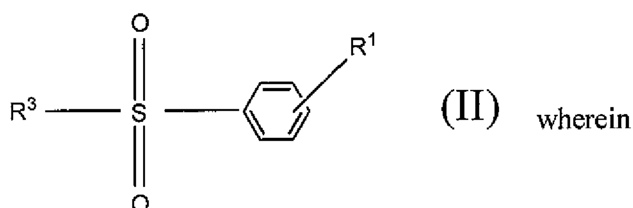
[0026] Among the compounds listed above, preferred compounds include NSC 743402, NSC 743403, NSC 743404, NSC 743407, NSC 743408, NSC 743409, NSC 743410, and NSC 743411. More preferred compounds include NSC 743404, NSC 743408, and NSC 743411, whose structures are set forth below, respectively. NSC 743411 is further preferred.

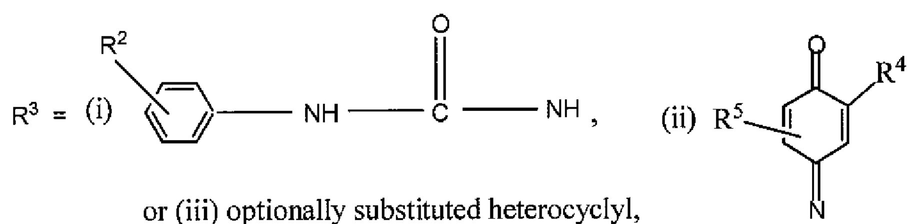


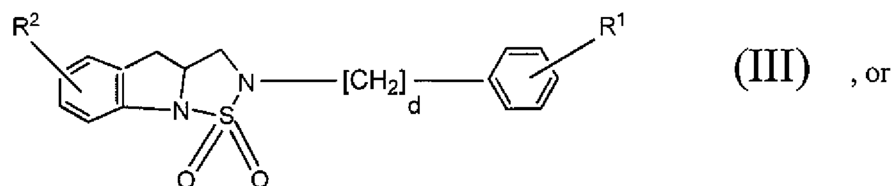
[0027] The above compounds, or prodrugs, salts, or solvates thereof, are targeted for use in the treatment of cancer, prevention of cancer, and in preventing the progress of development of precancerous lesions into cancer, wherein the cancer can be a cancer in any organ, for example, a cancer selected from the group consisting of glioma, thyroid carcinoma, breast carcinoma, small-cell lung carcinoma, non-small-cell carcinoma, gastric carcinoma, colon carcinoma, gastrointestinal stromal tumor, pancreatic carcinoma, bile duct carcinoma, CNS carcinoma, ovarian carcinoma, endometrial carcinoma, prostate carcinoma, renal carcinoma, anaplastic large-cell lymphoma, leukemia, multiple myeloma, mesothelioma, and melanoma, and combinations thereof, particularly a cancer selected from the group consisting of leukemia, non-small-cell carcinoma, breast carcinoma, colon carcinoma, CNS carcinoma, melanoma, ovarian carcinoma, renal carcinoma, and prostate carcinoma, more particularly, the cancer is a non-small-cell carcinoma, for example, a non-small-cell carcinoma characterized by a cell line selected from the group consisting of H1703, MB468, PC3, H460, and H157.

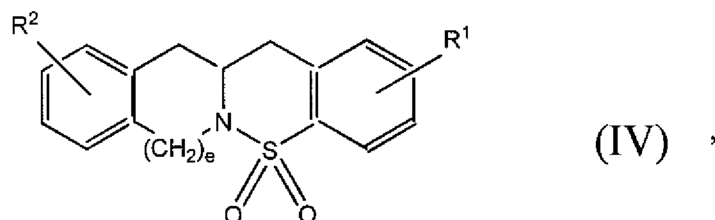
[0028] In accordance with another embodiment, the invention provides a method for inhibiting mTOR comprising administering an effective amount of a compound of formula (I), (II), (III), or (IV):











wherein A is C_6-C_{20} aryl, C_6-C_{20} aryl C_1-C_6 alkyl C_6-C_{20} aryl, heteroaryl, or heteroaryl C_1-C_6 alkyl, optionally further substituted, at the aryl, alkyl, or at the heteroaryl moiety, with one or more substituents selected from the group consisting of C_2-C_6 alkenyl,

halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and hydroxy C_1-C_6 alkyl;

R^1 is selected from the group consisting of C_1-C_6 alkyl, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and nitro;

R^2 is selected from the group consisting of hydrogen, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl;

R^4 is selected from the group consisting of carboxy C_1-C_6 alkyl, carboxy C_1-C_6 alkoxy, and carboxy C_1-C_6 alkylthio;

R^5 is hydrogen, C_6-C_{20} aryl which may be linked at one carbon atom or on two carbon atoms as fused, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl, which may be optionally substituted with a substituent selected from the group consisting of C_1-C_6 alkyl, halo, nitro, hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl; and

a, b, c, d, and e are independently 0 to 6;

or a prodrug, salt, or solvate thereof.

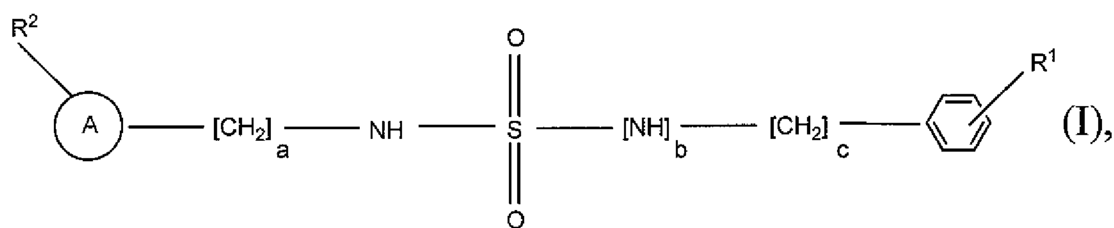
[0029] In another embodiment, the present invention provides a compound for inhibiting mTOR, wherein the compound is of formula (I), (II), (III), or (IV) above or a prodrug, salt, or solvate thereof.

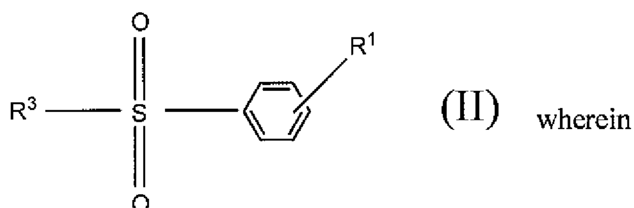
[0030] The compounds above or prodrugs, salts, or solvates thereof inhibit the activation of Akt, particularly Akt1 in certain cancer cell types. In an embodiment, the compounds inhibit the binding of Akt's pleckstrin homology (PH) domain to a phosphoinositide. In another embodiment, the compounds above activate AMP-activated protein kinase (AMPK).

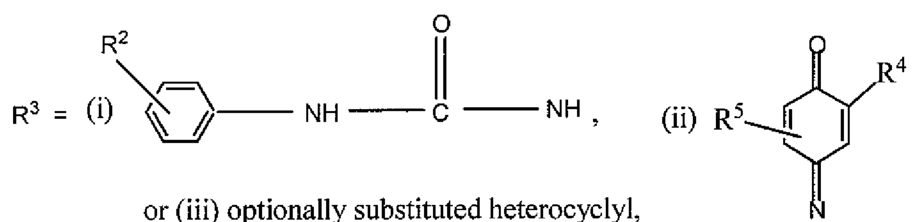
[0031] The above compounds, or prodrugs, salts, or solvates thereof, are targeted for use in the treatment of cancer, prevention of cancer, and in preventing the progress of development of precancerous lesions into cancer, wherein the cancer can be a cancer in any organ, for example, a cancer selected from the group consisting of glioma, thyroid carcinoma, breast carcinoma, small-cell lung carcinoma, non-small-cell carcinoma, gastric carcinoma, colon carcinoma, gastrointestinal stromal tumor, pancreatic carcinoma, bile

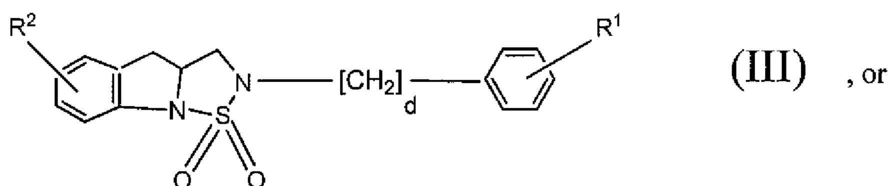
duct carcinoma, CNS carcinoma, ovarian carcinoma, endometrial carcinoma, prostate carcinoma, renal carcinoma, anaplastic large-cell lymphoma, leukemia, multiple myeloma, mesothelioma, and melanoma, and combinations thereof, particularly a cancer selected from the group consisting of leukemia, non-small-cell carcinoma, breast carcinoma, colon carcinoma, CNS carcinoma, melanoma, ovarian carcinoma, renal carcinoma, and prostate carcinoma, more particularly, the cancer is a non-small-cell carcinoma, for example, a non-small-cell carcinoma characterized by a cell line selected from the group consisting of H1703, MB468, PC3, H460, and H157.

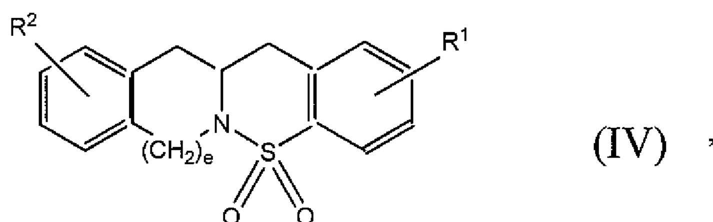
[0032] The present invention also provides a compound of one of formulas (I)-(IV):











wherein A is C_6-C_{20} aryl, C_6-C_{20} aryl C_1-C_6 alkyl C_6-C_{20} aryl, heteroaryl, or heteroaryl C_1-C_6 alkyl, optionally further substituted, at the aryl, alkyl, or at the heteroaryl moiety, with one or more substituents selected from the group consisting of C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and hydroxy C_1-C_6 alkyl;

R^1 is selected from the group consisting of C_1-C_6 alkyl, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and nitro;

R^2 is selected from the group consisting of hydrogen, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl;

R^4 is selected from the group consisting of carboxy C_1-C_6 alkyl, carboxy C_1-C_6 alkoxy, and carboxy C_1-C_6 alkylthio;

R^5 is hydrogen, C_6-C_{20} aryl which may be linked at one carbon atom or on two carbon atoms as fused, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl, which may be optionally substituted with a substituent selected from the group consisting of C_1-C_6 alkyl, halo, nitro, hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl; and

a, b, c, d, and e are independently 0 to 6;

or a prodrug, salt, or solvate thereof;

with the provisos that:

(a) in formula (I), when all of a, b, and c are 0 or 1 or when at least one of a, b, and c is 0 and at least one of the other is less than 2, and R^2 is alkenyl, then R^1 is not hydrogen, alkyl, halogen, alkoxy, nitro, or trifluoromethoxy;

(b) in formula (II), when R^3 is (i) and R^2 is alkenyl, then R^1 is not alkyl; when R^3 is (ii) and R^1 is ethoxy, R^4 is carboxy alkyl thio, R^5 is not benzo; when R^3 is (iii) optionally substituted heterocyclyl and R^1 is alkyl, then the substituted heterocyclyl is not an indole substituted with alkoxycarbonyl amino alkyl;

(c) in formula (III), when R^2 is hydrogen and d is 1, then R^1 is not hydrogen; and when R^2 is hydrogen and d is 0, then R^1 is not alkoxy; and

(d) in formula (IV), when R^2 is hydrogen and e is 0, then R^1 is not alkyl or alkoxy; and when R^2 is hydrogen and e is 1, then R^1 is not alkyl.

[0033] In accordance with any of the embodiments of the invention, the term "aryl" refers to a mono, bi, or tricyclic carbocyclic ring system having one, two, or three aromatic rings, for example, phenyl, naphthyl, anthracenyl, or biphenyl.

[0034] In accordance with the invention, the term "heteroaryl" refers to a cyclic aromatic radical having from five to ten ring atoms of which at least one atom is O, S, or N, and the remaining atoms are carbon. Examples of heteroaryl radicals include indolyl,

pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, and isoquinolinyl.

[0035] In accordance with an embodiment, the alkyl group is preferably a C_1-C_3 alkyl. Examples of alkyl group include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, and the like. This definition also applies wherever 'alkyl" occurs such as in hydroxyalkyl, monohalo alkyl, dihalo alkyl, and trihalo alkyl.

[0036] In accordance with an embodiment, the alkenyl group is preferably a C_2-C_4 alkenyl. Examples of alkenyl group include ethenyl, allyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, and the like.

[0037] In accordance with an embodiment, the alkoxy group is preferably a C_1-C_3 alkoxy. Examples of alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, tert-butoxy, n-pentoxy, isopentoxy, n-hexoxy, and the like.

[0038] The term "halo" refers to a halogen selected from the group consisting of fluorine, chlorine, bromine, and iodine, preferably chlorine or bromine.

[0039] Heterocyclyl groups include heteroaryl groups described above and further include cyclic groups, saturated or unsaturated, having a hetero atom. Examples of heterocyclyl groups include indolyl, pyridyl, piperidinyl, piperazinyl, pyrazinyl, pyrolyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolidinyl, furanyl, tetrahydrofuranyl, thiophenyl, tetrahydrothiophenyl, purinyl, pyrimidinyl, thiazolyl, thiazolidinyl, thiazolinyl, oxazolyl, triazolyl, tetrazolyl, tetrazinyl, benzoxazolyl, morpholinyl, thiophorpholinyl, quinolinyl, and isoquinolinyl, each of which may be optionally substituted with a substituent selected from the group consisting of C_1-C_6 alkyl, halo, nitro, hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino alkyl.

[0040] In any of the embodiments above, R^1 is preferably hydrogen, methyl, ethyl, nitro, methoxy, ethoxy, or trifluoromethyl.

[0041] In any of the embodiments above, R^2 is preferably allyl, bromo, hydroxymethyl, indolylmethyl, or indolylethyl.

[0042] In any of the embodiments above, R^4 is preferably carboxymethylthio or carboxyethylthio.

[0043] In any of the embodiments above, R^5 is preferably phenyl or benzo.

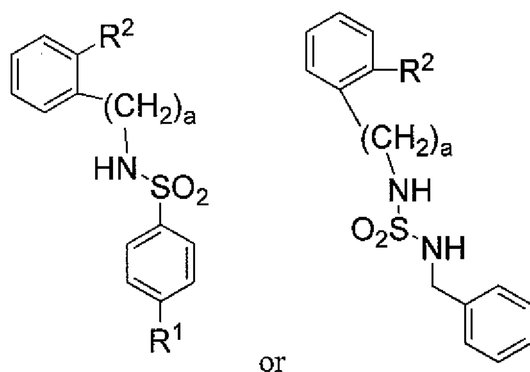
[0044] The alkyl, alkoxy, and alkylamino groups can be linear or branched. When an aryl group is substituted with a substituent, e.g., halo, amino, alkyl, hydroxyl, alkoxy, and others, the aromatic ring hydrogen is replaced with the substituent and this can take place in any of the available hydrogens, e.g., 2, 3, 4, 5, and/or 6-position wherein the 1-position is the point of attachment of the aryl group in the compound of the present invention.

[0045] The term "animal" refers to any member of the animal kingdom. In embodiments, "animal" refers to a human, at any stage of development. In embodiments, "animal" includes mammals, birds, reptiles, amphibians, fish, and worms. In certain embodiments, the non-human animal is a mammal, e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig. The animal may also be a transgenic animal, genetically engineered animal, or a clone.

[0046] In accordance with an embodiment of the invention, the method involves administering a compound of formula (I), or a prodrug, salt, or solvate thereof, wherein a, b, and c are 0. In another embodiment, the method involves administering a compound of formula (I), or a prodrug, salt, or solvate thereof, wherein a, b, and c are 1. In a further embodiment, the method involves administering a compound of formula (I), or a prodrug, salt, or solvate thereof, wherein a is 0 and b and c are 0. In yet another embodiment, the method involves administering a compound of formula (I), or a prodrug, salt, or solvate thereof, wherein a and c are 0 and b is 1.

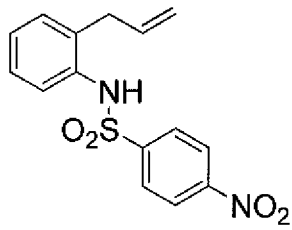
[0047] In another embodiment, the method involves administering a compound of formula (II), or a prodrug, salt, or solvate thereof, wherein a, b, and c are 0.

[0048] Examples of compounds of formula I include those of the structures

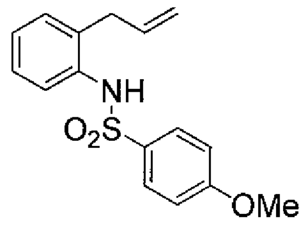


wherein a, R^1, and R^2 are defined above.

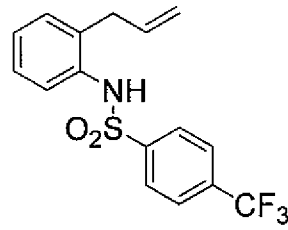
[0049] Specific examples of compounds of formula I include:



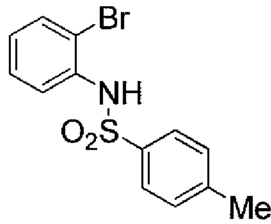
sulfonamide-1,



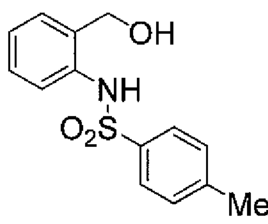
sulfonamide-2,



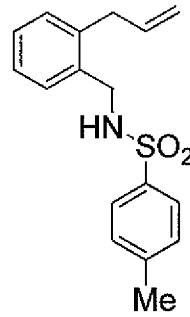
sulfonamide-3,



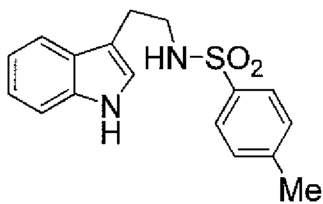
sulfonamide-4,



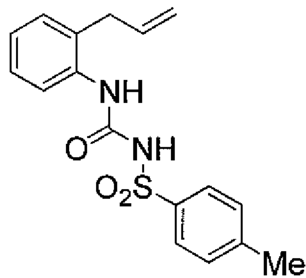
sulfonamide-5,



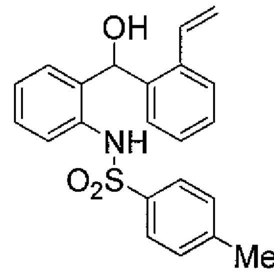
sulfonamide-6,



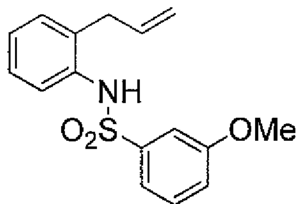
sulfonamide-7,



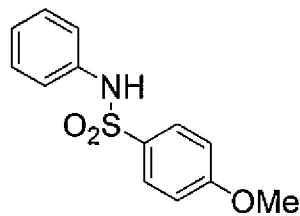
sulfonamide-9,



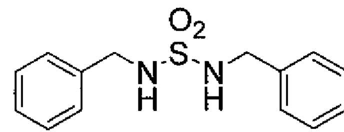
sulfonamide-10,



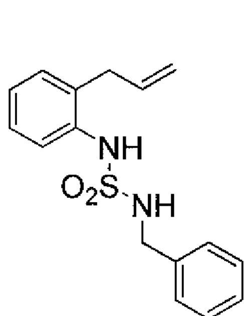
sulfonamide-11,



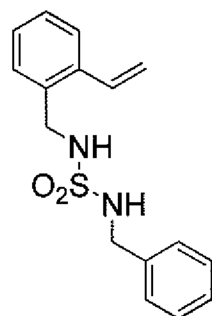
sulfonamide-12,



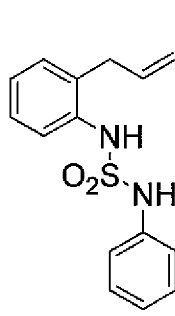
sulfamide-1,



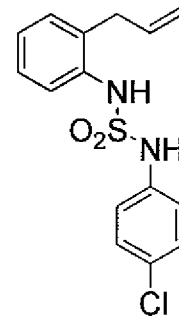
sulfamide-2,



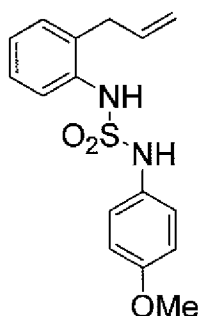
sulfamide-3,

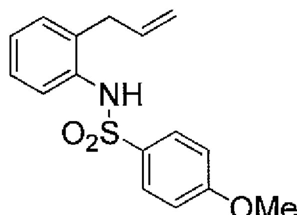


sulfamide-5,



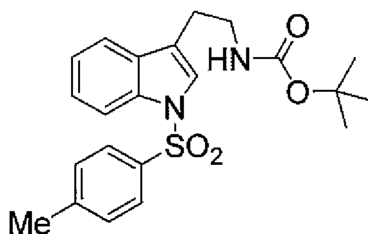
sulfamide-6,





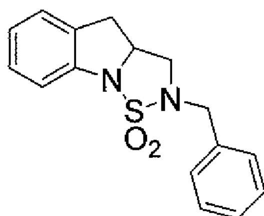
and sulfamide-7, particularly sulfonamide-2.

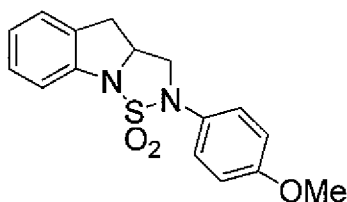
[0050] A specific example of compound of formula II includes:



sulfonamide-8.

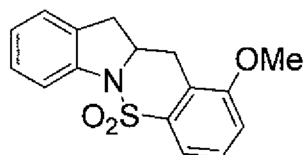
[0051] Specific examples of compounds of formula III include:

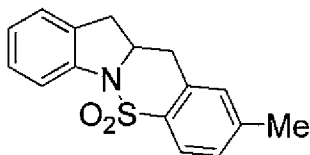


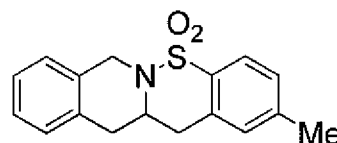


sulfamide-4 and sulfamide-8.

[0052] Specific examples of compounds of formula IV include







sultam-1, sultam-2, and sultam-3.

[0053] The invention also provides a pharmaceutical composition comprising a compound, prodrug, salt, or solvate described above and a pharmaceutically acceptable carrier.

[0054] The term "prodrug" denotes a derivative of a compound, which derivative, when administered to warm-blooded animals, e.g. humans, is converted into the compound (drug). The enzymatic and/or chemical hydrolytic cleavage of the compounds

of the present invention occurs in such a manner that the proven drug form (parent carboxylic acid drug) is released, and the moiety or moieties split off remain nontoxic or are metabolized so that nontoxic metabolic products are produced. Non-limiting examples include esters, amides, ethers, and carbonates.

[0055] The phrase "salt" or "pharmaceutically acceptable salt" is intended to include nontoxic salts synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, and *Journal of Pharmaceutical Science*, *66*, 2-19 (1977). For example, they can be a salt of an alkali metal (e.g., sodium or potassium), alkaline earth metal (e.g., calcium), or ammonium of salt.

[0056] The compounds of the various embodiments of the invention can be obtained from commercial sources or synthesized following procedures taught in the literature, for example, Zawaba, T. P., et al., *J. Am. Chem. Soc.*, 2005, *127*, 11250-11251 and supplemental materials S1-S28; Zawaba, T. P., et al., *Organic Letters*, 2007, *9*, 2035-2038 and S1-S28; Sherman, E. S., et al., *Organic Letters*, 2004, *6*, 1573-1575 and S1-S10; Sherman, E. S., et al., *J. Org. Chem.*, 2007, *72*, 3896-3905 and S1-S36.

[0057] In embodiments involving compounds of formulas (I)-(IV), or prodrugs, salts, or solvates thereof, the cancer is characterized by any suitable cell line, particularly A549 and H1703 cell lines. Preferably, the compound of formulas (I)-(IV) arrest the G2/M phase of the cancer cell cycle.

[0058] Whenever a range of the number of atoms in a structure is indicated (e.g., a C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_3 alkyl, haloalkyl, alkylamino, alkenyl, etc.), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-8 carbon atoms (e.g., C_1-C_8), 1-6 carbon atoms (e.g., C_1-C_6), 1-4 carbon atoms (e.g., C_1-C_4), 1-3 carbon atoms (e.g., C_1-C_3), or 2-8 carbon atoms (e.g., C_2-C_8) as used with respect to any chemical group (e.g., alkyl, haloalkyl, alkylamino, alkenyl, etc.) referenced herein

encompasses and specifically describes 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 2-7 carbon atoms, 2-8 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms, 4-7 carbon atoms, 4-8 carbon atoms, 5-6 carbon atoms, 5-7 carbon atoms, 5-8 carbon atoms, 6-7 carbon atoms, or 6-8 carbon atoms, as appropriate).

[0059] In any of the above embodiments of the invention, the compounds, or a prodrugs, salts, or solvates thereof, preferably inhibit the binding of Akt's pleckstrin homology (PH) domain to a phosphoinositide.

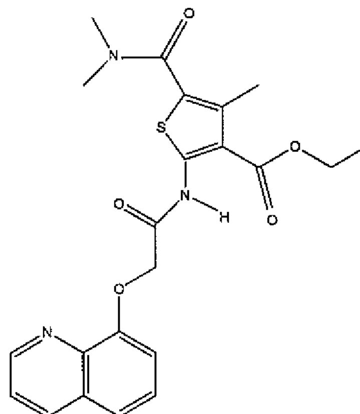
[0060] In any of the embodiments of the invention, the cancer can be any cancer in any organ, for example, a cancer is selected from the group consisting of glioma, thyroid carcinoma, breast carcinoma, small-cell lung carcinoma, non-small-cell carcinoma, gastric carcinoma, colon carcinoma, gastrointestinal stromal carcinoma, pancreatic carcinoma, bile duct carcinoma, CNS carcinoma, ovarian carcinoma, endometrial carcinoma, prostate carcinoma, renal carcinoma, anaplastic large-cell lymphoma, leukemia, multiple myeloma, mesothelioma, and melanoma, and combinations thereof.

[0061] In any of the embodiments above, the method can be carried out in conjunction with another cancer therapy. For example, the another cancer therapy comprises chemotherapy, radiation therapy, or biological therapy. In an embodiment, the biological therapy involves administration of a protein, which may be an antibody or a recombinant protein. The combination therapy can be carried out such that the two therapies can be administered simultaneously or sequentially, and when administered sequentially, in any order, i.e., a radiation therapy, biological therapy, or a conventional chemotherapeutic agent first followed by the administration of the compound of the invention, or a compound of the invention administered first followed by radiation therapy, biological therapy, or administration of the conventional chemotherapeutic agent.

[0062] In a particular embodiment, the another cancer therapy comprises chemotherapy, which could involve the administration of any suitable chemotherapy agent, for example, an agent selected from the group consisting of abarelix, aldesleukin, alemtuzumab, altretamine, amifostine, aminoglutethimide, anastrazole, arsenic trioxide,

asparaginase, azacitidine, azathioprine, BCG vaccine, bevacizumab, bexarotene, bicalutamide, bleomycin sulfate, bortezomib, bromocriptine, busulfan, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, chloroquine phosphate, cladribine, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, daunorubicin citrate liposomal, dexrazoxane, docetaxel, doxorubicin hydrochloride, doxorubicin hydrochloride liposomal, epirubicin hydrochloride, estramustine phosphate sodium, etoposide, estretinate, exemestane, floxuridine, fludarabine phosphate, fluorouracil, fluoxymesterone, flutamide, fulvestrant, gefitinib, gemcitabine hydrochloride, gemtuzumab ozogamicin, goserelin acetate, hydroxyurea, idarubicin hydrochloride, ifosfamide, imtinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan hydrochloride trihydrate, letrozole, leucovorin calcium, leuprolide acetate, levamisole hydrochloride, lomustine, lymphocyte immune anti-thymocyte globulin (equine), mechlorethamine hydrochloride, medoxyprogestone acetate, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone hydrochloride, nilutamide, oxaliplatin, paclitaxel, pegaspargase, pentostatin, plicamycin, porfimer sodium, procarbazine hydrochloride, streptozocin, tamoxifen citrate, temozolomide, teniposide, testolactone, testosterone propionate, thioguanine, thiotepa, topotecan hydrochloride, tretinoin, uracil mustard, valrubicin, vinblastine sulfate, vincristine sulfate, and vinorelbine.

[0063] The present invention further provides a method of treating an animal for a disease or adverse condition that responds to inhibiting the activity of CSF1R receptor comprising administering to the animal an effective amount of the compound of the formula or a prodrug, salt, or solvate thereof,



so that the disease or the adverse condition is treated. Examples of such disease or adverse condition include chronic myelomonocytic leukemia, Alzheimer's disease, and brain injury.

[0064] In accordance with the embodiments of the invention, the compounds, or prodrugs, salts, or solvates thereof, can be administered as such or in the form of a pharmaceutical composition. The pharmaceutical composition comprises at least one compound, or a prodrug, salt, or solvate thereof, and a pharmaceutically acceptable carrier. Advantageously, the pharmaceutical composition may include two, three or more agents, at least one of which is a compound of the invention as described above, in combination with one or more conventional chemotherapeutic agents.

[0065] The pharmaceutically acceptable carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration. It will be appreciated by one of skill in the art that, in addition to the following described pharmaceutical compositions; the compounds, salts, or conjugates of the present invention can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes.

[0066] The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, or diluents, are well known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active compounds and one which has no detrimental side effects or toxicity under the conditions of use.

[0067] The choice of carrier will be determined in part by the particular active agent, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following formulations for topical, oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular, intratumoral, peritumoral, interperitoneal, intrathecal, rectal, and vaginal administration are merely exemplary and are in no way limiting.

[0068] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound, salt, or conjugate dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each

containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

[0069] The compounds, or prodrugs, salts, or solvates thereof, of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

[0070] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound, or a prodrug, salt, or solvate thereof, can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or

polyethylene glycol, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0071] Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene-polypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (3) mixtures thereof.

[0072] The parenteral formulations will typically contain from about 0.5 to about 25% by weight of the compound, or a prodrug, salt, or solvate thereof, in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections,

immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0073] The compounds, prodrugs, salts, or solvates thereof, may be made into injectable formulations. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J. B. Lippincott Co., Philadelphia, Pa., Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986).

[0074] Additionally, the compounds, prodrugs, salts, or solvates thereof may be made into suppositories by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

[0075] The compounds can be used in any suitable dose. Suitable doses and dosage regimens can be determined by conventional range finding techniques. Generally treatment is initiated with smaller dosages, which are less than the optimum dose. Thereafter, the dosage is increased by small increments until optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In proper doses and with suitable administration of certain compounds, the present invention provides for a wide range of responses. Typically the dosages range from about 0.001 to about 1000 mg/kg body weight of the animal being treated/day.

[0076] For example, in embodiments, the compounds, products, salts, or solvates may be administered from about 100 mg/kg to about 300 mg/kg, from about 120 mg/kg to about 280 mg/kg, from about 140 mg/kg to about 260 mg/kg, from about 150 mg/kg to about 250 mg/kg, from about 160 mg/kg to about 240 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. In preventing the development or preventing the progression of precancerous lesions into cancer, the compounds, prodrugs, salts, or solvates may be administered at a lower dosage, for example, from about 1 mg/kg to about 80 mg/kg, from about 5 mg/kg to about 70 mg/kg, from about 10 mg/kg to about 70 mg/kg, from about 10 mg/kg to about 60 mg/kg, from

about 20 mg/kg to about 70 mg/kg, from about 20 mg/kg to about 60 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired effect.

[0077] The treatment can be prophylactic or therapeutic. By "preventing the progression" is meant any degree (10, 20, 30, 40, 50, 60, 70, 80, 90% or more) in inhibition of the onset of cancer or progression of precancerous lesions into cancer, including complete inhibition. By "treatment" is meant any degree (10, 20, 30, 40, 50, 60, 70, 80, 90% or more) in inhibition of the growth or metastasis of the cancer in the animal (e.g., human).

[0078] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0079] This example demonstrates the various methods and materials employed in the present invention and the biological activities of compounds in accordance with an embodiment of the invention.

[0080] NSCLC cell lines H157, H1703, H460, PC3 and MDA MB468 were grown and maintained in RPMI 1640 (Life Technologies, Gaithersburg, MD) plus 5 or 10% fetal bovine serum and 50 ug/mL gentamycin. For low serum conditions, the serum concentration was reduced to 0.1% FBS.

[0081] *Reagents.* Antibodies for western blot analysis were purchased from Cell Signaling Technology (Beverly, MA) except total Akt antibody (BD biosciences, San Jose, CA). Secondary antibodies used for immunofluorescence were anti-mouse Alexa-fluor488 and anti-rabbit Alexa-fluor568 (Molecular Probes). AMPK antibody and secondary antibody were from Cell Signaling. IR dye-linked antibodies were from Invitrogen (Carlsbad, CA). LY294002 was purchased from Calbiochem EMD Biosciences, Inc. (La Jolla, CA), recombinant human EGF from R & D Systems (Minneapolis, MN) and 105 compounds identified in the *in silico* screen were procured through ChemNavigator (San Diego, CA). All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO).

[0082] *Pharmacologic Treatments.* For secondary screening in H157, cells were plated at 5.0 x 10^5 cells/well in 6-well plates in RPMI containing 5% FBS. Each well was rinsed with and changed to RPMI containing 0.1% FBS immediately prior to treatment. In

all experiments, DMSO was added to one sample as a negative control and LY294002 as the positive control.

[0083] *Immunoblotting.* Cell extracts were prepared in 4% SDS. Lysates were sonicated for 15s with a Vibra Cell sonicator. Lysates were size separated by polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride (PVDF) membranes. Membranes were blocked for 10 min in Li-Cor Blocking Buffer (Lincoln, NE) and incubated with primary antibody diluted in the same plus 0.05% triton X100. Primary antibodies were detected using an IR dye-linked antibodies (Invitrogen). Detection of pS473 and total Akt were done simultaneously using two different primary antibody species and secondary antibodies of different wavelengths for simultaneous two-color detection using an Odyssey infrared scanner (Licor, Lincoln, NE). Immunoblot experiments were performed at least three times.

[0084] *NCI 60 Cell Line Screen.* Upon submission for testing, each compound was given a unique NSC number by the National Cancer Institute, Developmental Therapeutics Program. Tested compounds were identified by this number in all future experiments. Methods for evaluation of cell growth inhibition in the NCI 60 cell line panel were published previously (Kumar et al., *Oncogene 24*: 7493-7501; Luo et al., *Cancer Cell 4*: 257-262, 2003). Briefly, the compounds were dissolved in DMSO, diluted into RPMI 1640 + 5% fetal bovine serum, and added to 96-well plates containing cell lines that were previously cultured for 24 hours. After a 48-hour incubation with the inhibitors, the media were removed, and the cells were fixed and stained with sulforhodamine B. Unbound dye was removed with five washes of 1% acetic acid, and the plates were allowed to air dry. The dye was resolubilized in Tris buffer, and the absorbance at 515 nm was measured. The concentration that produced 50% growth inhibition compared with a DMSO control (GI_{50}), total growth inhibition (or 0% growth) compared with a DMSO control (TGI), and the concentration that produced death of 50% of the cells present at the start of the experiment (LC_{50}) were determined.

[0085] *Apoptosis and Death Assays.* After treatment of cells for varying times, floating cells were collected and added to adherent cells following harvest by trypsinization. An aliquot was stained with 5 μg/ml propidium iodide and at 10,000 cells per sample were analyzed by flow cytometry. Remaining cells were fixed in 70% ethanol overnight, rinsed with PBS and incubated with propidium iodide (5 μg/ml) supplemented

with RNAase A (30 μg/ml) for 30 min at room temperature for 5 min followed by flow cytometry using a Becton Dickinson FACSort (San Jose, CA). Sub-2N DNA population percent was determined by gating using FlowJo software (Tree Star, Inc. Ashland, OR).

[0086] *Translocation Assays.* H157 cells seeded on cover slips in 6-well plates were treated with potential Akt inhibitors for 4 hours in 0.5% FBS and 100 ng/ml EGF was added to activate Akt 15 min prior to fixation with 10% neutral buffered formalin for 20 min. After fixation, cells were stored in 70% ethanol at 4 °C overnight. Prior to staining, cells were washed 4 times with PBS, blocked in 2% BSA for 30 min, and probed with pS473 mouse monoclonal antibody and total Akt rabbit polyclonal antibody for 4h at room temp in 0.5% BSA, 0.05% tween in PBS. After washing, cover slips were stained with fluorescent secondary antibodies and Dapi to stain nuclei. Fluorescence was visualized with laser scanning confocal microscopy (Zeiss, Thornwood, NY).

[0087] In vivo *biomarker validation.* Studies were done under an approved National Cancer Institute animal study proposal in accordance with the Guide for the Care and Use of Laboratory Animals. Three 6-week-old A/J female mice were injected with a single intraperitoneal dose of 25 mg/kg NSC 743411. Drug was dissolved in DMSO at 100 mg/ml and diluted 1:40 in 5% Tween 80, 5% PEG 4000. Three matched mice received a single dose of the vehicle only. At 4h, 8h and 24h after injection 3 drops of blood were bled from the mandibular vein into 1 ml of ice-cold ACK lysing buffer. After 5 min incubation on ice, cells were pelleted and lysed with 50 μl of SDS lysis buffer, sonicated and subjected to Western blot analysis as above.

[0088] In vivo *tumor studies.* Studies were done under an approved National Cancer Institute animal study proposal in accordance with the Guide for the Care and Use of Laboratory Animals. Six-week old, athymic nude mice were implanted with $1x10^7$ H1703 cells (w/ 50% matrigel) in the right flank. Tumors were allowed to grow for 27 days. Animals were randomized into three groups: Vehicle (10% DMSO, 5% PEG 4000, 5% Tween-80 in saline), 5mg/kg, AND 50mg/kg (n=3 per group). Drug was dissolved in DMSO at 100 mg/ml and diluted 1:40 in 5% Tween 80, 5% PEG 4000. Daily intraperitoneal injections of vehicle or NSC 743411 were administered for 5 days (Day 27 through Day 31). Tumor volume and body weight were monitored using standard techniques.

[0089] Xenograft tumors were harvested and frozen in liquid nitrogen. Samples were homogenized, resuspended in RIPA lysis buffer, and western blot analysis performed (15μg protein).

[0090] *Ambit Kineome scan.* High throughput screening for kinase domain interactions was performed for NSC 743404, NSC 743408 and NSC 743411 using Kineome scan 96 as described previously (Karaman et al., *Biotechnol 26*: 127-132, 2008).

[0091] *Cell-based screening.* 105 compounds were identified by *in silico* screening as potential inhibitors of Akt. The test compounds were subjected to a cell-based secondary screen where levels of phosphorylated and total Akt were assessed in NSCLC cell lines. H157 cells were chosen as the initial test cell line due to high levels of endogenous active Akt, which is likely related to absent PTEN function. The test compounds (10 μM) were incubated on cells for 2 hr, because this time is adequate for ≥80% inhibition of S473 phosphorylation in H157 cells by other inhibitors of the pathway. Cells were cultured in 0.5% FBS to minimize potential loss from protein binding. Each set of experiments included a DMSO (solvent) negative control, and the PI3K inhibitor, LY294002, as a positive control. Akt inhibition was calculated as the relative decrease in the pS473/total Akt ratio compared with the DMSO negative control, and was visibly apparent as a decrease in green signal (pS473). 21 of 105 (20%) compounds inhibited Akt phosphorylation in this secondary screen, which is a large improvement over random screening protocols. In addition to Akt inhibitors, 4 Akt activators were identified (data not shown). These 25 Akt inhibitors and activators were tested in another cell line with wild type PTEN (H1703). Surprisingly, two of the compounds that activated Akt in H157 cells inhibited Akt in H1703 cells (Table 1).

[0092] Table 1. Akt inhibitors identified by *in vitro* screening on H1703, MB468, PC3, H460 and H157 non-small cell lung cancer cell lines. A (-) indicates Akt inhibition and (n) indicates no change, as measured by change in S473 phosphorylation on western blots. GI50 and LC50, the average concentration (μM) giving 50% growth inhibition (GI) or death (LC) in the NCI60 cell lines.

NSC #	H1703	MB468	PC3	H460	H157	GI50	LC50
743402	-	-	-	-	n	30	>100
743403	-	n	-	-	-	97.7	>100
743404	-	+	-	n	n	18.2	91.2
743405	-	-	-	-	n	>100	>100
743406	-	n	-	-	-	>100	>100
743407	-	-	-	-	-	41.7	97.7
743408	-	-	-	n	-	13.5	91.2
743409	-	-	-	-	+	24.5	97.7
743410	-	-	-	-	n	>100	>100
743411	-	-	+	-	+	3.98	43.7

[0093] NSC 743411 activates AMPK. AMPK and Akt are upstream of mTOR. Activation of AMPK negatively regulates mTOR independently of Akt inhibition, which also negatively regulates mTOR. Activation of AMPK and inhibition of Akt with NSC 743411 occur with similar dose- and time-dependence. Simultaneous inhibition of Akt and activation of AMPK would likely result in profound inhibition of mTOR and enhance the anticancer activity.

[0094] *Anticancer Activity and PH-domain specificity.* To assess the potential utility of these compounds as cancer therapeutics, the 10 compounds above were screened for growth inhibition and cell killing in the NCI 60 cell line panel. Three compounds, NSC 743404, NSC 743408 and NSC743411 were effective at inhibiting the growth of all of the cell lines, with the GI50s in the low micro-molar range for most cell lines (Table 1). In untreated cells, pS473-Akt is predominantly cytoplasmic but upon growth factor stimulation, Akt is translocated to the cell membrane due to binding of PIP3 to its PH-domain. To assess the effects of the lead compounds on Akt translocation, EGF was added to H157 cells and the localization of phosphorylated Akt was assessed using

immunofluorescence. Each lead compound (NSC 743404, NSC 743408 and NSC 743411) prevented membrane association of active Akt in response to EGF, similar to the effects of LY294002. Inhibition of active Akt localization by LY294002 works indirectly through the PH domain by decreasing phosphoinositide levels. This suggested that the test compounds are working either directly or indirectly through the PH-domain of Akt since inhibition by other mechanisms would not be expected to alter the membrane localization.

[0095] NSC 743411 was the most potent compound tested in the NCI 60 cell line screen, (Fig. 5), while the composite dose-response curves were similar for NSC 743404 and NSC 743408. For the majority of the cell lines, NSC743411 exhibited little or no inhibition of proliferation at 1 μM, but had near complete growth inhibition or cytotoxicity at 10 μM. The average GI50 for NSC 743411 was approximately 4 μM; the average LC50 was 43.7 μM. However, more than 30% of the cell lines had total growth inhibition at doses of 10 μM or less (Fig 5, Table 1). Due to its superior broad-range cytotoxicity, NSC743411 was chosen for further investigation.

[0096] *NSC 743411 induces non-apoptotic cell death.* H1703 cells have high levels of constitutively active Akt and depend upon Akt for survival. Morphological changes consistent with cytotoxicity were apparent in multiple cell lines treated with NSC 743411, but H1703 appeared to be among the most sensitive. By 24 h, nearly 50% of cells were dead as measured by propidium iodide staining, which requires membrane permeability that is absent in viable cells (Fig. 6A). However, less than 5% percent of cells were apoptotic at this time, as measured by sub-G1 DNA content on flow cytometry (Fig. 6B). Morphologically, cells treated with NSC 743411 for 24 h were refractile and rounded, although mostly still attached, with prominent membrane blebs (Fig. 6C). By 48 h, nearly all of the cells were dead although there was no increase in apoptotic cells (Figs. 6A and B).

[0097] *NSC 743411 Inhibits Akt in a Dose- and Time-Dependent Manner.* Since Akt inhibition was initially assessed at a single dose and time, additional studies were conducted to determine the dose and time dependence of Akt inhibition by NSC 743411. First, the efficacy of NSC 743411 was assessed in 5% FBS. NSC 743411 inhibited Akt equally well in 0.5% FBS or 5% FBS; thus, all subsequent experiments were performed in 5% FBS. Upon treatment of H1703 cells for 8 h with NSC 743411, Akt phosphorylation was decreased with concentrations as low as 10 μM. NSC 743411 decreased Akt

phosphorylation without affecting total levels of Akt in four NSCLC cell lines (Table 1). Inhibition was observed as early as 6 h with 10 μM NSC743411, and was sustained for at least 24 hours after treatment, although many cells appeared dead at this time. At 20 uM, Akt inhibition was observed as early as 2h. To verify that loss of Akt phosphorylation on S473 was coupled with loss of Akt kinase activity, immunoblots were also probed with antibodies to assess phosphorylation of Akt downstream targets. GSK-3ab (S9/21) is a direct substrate of Akt, whereas pS6 (S235/236) is indirectly phosphorylated following Akt-dependent activation of mTOR and subsequently, S6-kinase. 4EBP-1 is another substrate of mTOR. Phosphorylation of each downstream substrate decreased concomitantly and commensurately with Akt inhibition. 4EBP1 dephosphorylation leads to an increase in electrophoretic mobility. Only a small amount of Parp cleavage, a marker for apoptosis, was observed, consistent with mostly non-apoptotic cell death induced by NSC743411 (Fig. 6B).

[0098] *Inhibition of Akt* in vivo. Preliminary experiments were performed with NSC 743411 to test for *in vivo* inhibition of Akt phosphorylation. Three mice were injected with a single dose of 25 mg/kg NSC 743411 intraperitoneally. PBMC lysates showed decreased Akt phosphorylation 4 h after NSC743411 injection as compared with vehicle-injected mice (Fig. 7), suggesting that the compound is bioavailable. However, due to the small sample size, this inhibition was not statistically significant. No adverse health effects of the drug were observed either acutely or up to one month following injection.

[0099] *NSC 743411 suppresses tumor growth* in vivo *and has limited toxicity* in vivo. See Figs. 8 and 9. There is no statistical difference between vehicle and 5 mg/kg but there is between vehicle and 50 mg/kg.

[0100] *NSC 743411 does not inhibit Akt via the kinase domain.* Akt inhibition by the lead compounds should not be via the Akt kinase domain since these compounds were specifically screened for binding to the PH domain. To confirm this, NSC 743404, NSC 743408 and NSC743411 were subjected to the Ambit Kineome scan 96, which tests inhibition of ATP binding to active sites of a panel of 96 kinases. This approach has been shown to be an excellent predictor of kinase inhibition by small molecules. None of the 3 lead compounds inhibited binding of ATP to Akt1 or Akt2, as expected for a PH-domain selective inhibitor. In addition, upstream activators of Akt such as PI3K, EGFR and HER2 also were not inhibited, suggesting that Akt inhibition is not due to inhibition of

upstream activators. Overall, NSC 743408 and NSC743411 had no activity for any of the kinases on the panel, but NSC 743404 inhibited CSF1R binding to ATP by 97% but had no activity for other kinases.

[0101] *Compare analysis.* The large amount of data obtained with the NCI 60 cell lines allows comparisons of new data sets with existing data sets on over 100,000 drugs and molecular targets. Using the COMPARE algorithm on the NCI website, NSC 743411 sensitivity did not correlate significantly with pS473-Akt but did correlate significantly with Akt1 protein levels (data set MT1368) (Pearson correlation coefficients: 0.291 NSC 743411 GI50 vs. Akt1, 0.356 NSC 743411 TGI vs. Akt1, 0.327 NSC 743411 LC50 vs. Akt1). The modeling and *in silico* screening were done using the PH domain of Akt1 which is consistent with Akt1 being a target of NSC743411. Since pS473-Akt represents active Akt1, Akt2 and Akt3, the lack of correlation with total pS473-Akt is not inconsistent with NSC743411 targeting the PH domain of Akt1.

[0102] Eleven compounds were chosen for further testing based on Akt inhibition in multiple cell lines. However, NCI 60 toxicity testing yielded only 3 compounds with the desired growth inhibition or cytotoxic activity in the 3-day assay. This may be due to instability of the compounds in culture, resulting in transient Akt inhibition and consequent limited cell growth inhibition and death. A time course for Akt inhibition was performed with NSC 743411, the most toxic in the NCI 60 screen, which showed prolonged Akt inhibition coupled with substantial cell killing occurring within 24 hours. Although NSC743411 elicited substantial cell death by 24 h in culture, little classical apoptosis was observed (Fig. 6B). Notably, the activity of NSC743411 in Akt inhibition and cell killing in 10% fetal bovine serum suggests that it has potential for activity under physiological conditions. In support of this, a small *in vivo* study showed that 25 mg/kg of NSC743411 can inhibit pS473-Akt in PBMCs 4 h after intraperitoneal injection in mice (Fig. 7) with no obvious adverse health effects.

[0103] Inhibition of Akt by a PH-domain-directed compound could prevent membrane localization of pS473-Akt, which was in fact observed after treatment of cells with NSC743411. Cytoplasmic localization was also reduced, coupled with intense nuclear staining suggesting that NSC 743411 also effects nuclear/cytoplasmic transport of active Akt. Nuclear Akt has been shown to localize with nuclear PML bodies where it is dephosphorylated by co-localized PP2A. Lack of inhibition of Akt1 or Akt2 in the Ambit

Kineome scan also suggests that inhibition is mediated through a domain other than the kinase domain. This assay also suggested that Akt inhibition is not mediated indirectly through inhibition of upstream components since PI3K, and upstream activators of PI3K, were not affected by NSC743411. This data is consistent with specificity of NSC 743411 for the PH domain of Akt.

[0104] The widespread use of the NCI 60 cell lines and the considerable molecular target information available for those cell lines makes the NCI 60 database a valuable resource to look for molecular correlates to drug sensitivity. The finding that NSC743411 toxicity correlated with Akt1 protein levels is consistent with NSC 743411 targeting Akt1. Even though NSC 743411 toxicity did not correlate significantly with pS473-Akt levels, other *in vitro* data support the PH domain specificity of this compound. EGF treatment leads to primarily membrane localization of active Akt in H157 cells, which is inhibited by NSC743411. However, the relative contribution of active Akt1, 2 and 3 to total active Akt in untreated and EGF-treated cells in unknown. It is possible that NSC 743411 only targets the PH domain of Akt1, and that active Akt1 may be more important for survival of tumor cell lines than the other Akt family members, Akt2 and Akt3. Active Akt1 has been shown to be oncogenic, and genetic deletion of Akt can prevent tumorigenesis in mice. A mutation in the PH domain of Akt1 was described in breast, colorectal, and ovarian tumors and squamous cell carcinomas of the lung. This mutation causes increased localization of Akt1 to the membrane and can transform fibroblasts in culture and cause leukemia in mice. Conversely, deletion of Akt1 alone can prevent tumor formation in mouse models suggesting that inhibition of Akt1 may be a potential strategy for tumor prevention and therapy.

[0105] The lead compound, NSC 743411, inhibited Akt phosphorylation, prevented phosphorylated Akt from localizing to the membrane and led to inhibition of growth and increased cell death in a variety of tumor types at physiologically achievable doses.

EXAMPLE 2

[0106] This example illustrates the activity of a compound in accordance with an embodiment of the invention. Compounds designated as sulfonamide-1 to sulfonamide-12, sulfamide-1 to sulfamide-8, and sultam-1 to sultam-3 were tested on H157, A549, and H1703 cell lines. H157 is a lung adenocarcinoma cell line with P-Akt+, p53 codon 285 CAG--AAG; A549 is a lung adenocarcinoma cell line, P-Akt-, p53 wild type; H157 is a

lung squamous carcinoma cell line, P-Akt+, p53 nonsense mutation at codon 298. The cells were exposed for 2 hours at 25 μM of the compounds. Immunoblotting results are shown in Tables 2-3. The sultam compounds either activated or showed no inhibition of Akt.

[0107] Table 2. Akt inhibiting activity of sulfonamides (1 to 12): + means activation; - means inhibition; S means no change in Akt.

Cells	1	2	3	4	5	6	7	8	9	10	11	12
H157 0.1% FBS	+	S	+	S	+	S	+	+	S	+		
H157 10% FBS	S	S	+	+	+	+	+	+	+	+		
A549 0.1% FBS	+	+	+	S	S	S	S	S	+	+	S	S
A549 10% FBS	S	-	-	-	S	S	S	+	+	+	S	S
H1703 0.1% FBS	+	S	+	+	+	S	S	+	+	+	S	S
H1703 10% FBS	S	-	S	S	S	-	S	+	+	+	S	S

[0108] Table 3. Akt inhibiting activity of sulfamides (1 to 8): + means activation; - means inhibition; S means no change in Akt

Cells	1	2	3	4	5	6	7	8
H157 0.1% FBS	S	S	S	S				
H157 10% FBS	S	S	S	S				
A549 0.1% FBS	S	S	+	+	S	S	S	S
A549 10% FBS	-	-	-	-	S	S	S	S
H1703 0.1% FBS	S	+	+	+	S	S	S	S
H1703 10% FBS	S	S	+	S	S	S	S	S

EXAMPLE 3

[0109] This example illustrates some other properties of sulfonamide-2 as shown in Figures 10-16. The compound inhibited the growth of A549 cells as shown by the change in cell morphology depicted in Fig. 10. The GI50 values are shown in Fig. 11. The sulfonamide also arrests the G2/M phase of cell growth as shown in Fig. 12. The sulfonamide causes G2/M phase arrest and increases acetylated tubulin expression of A549 cells as shown in Fig. 13. The sulfonamide also caused nonapoptotic cell death on H1703 cells (p53-) as shown in Figs. 14-16. It is believed that the cell death results from abnormal mitosis, thus causing mitotic catastrophe.

EXAMPLE 4

[0110] This example illustrates a biological activity of a compound in accordance with an embodiment of the invention. NSC 743404 was put through an Ambit kineome

(kinase) screen and it was found that the compound had significant activity against CSF1R, 6.3% of control. The compound was tested at 10 μM.

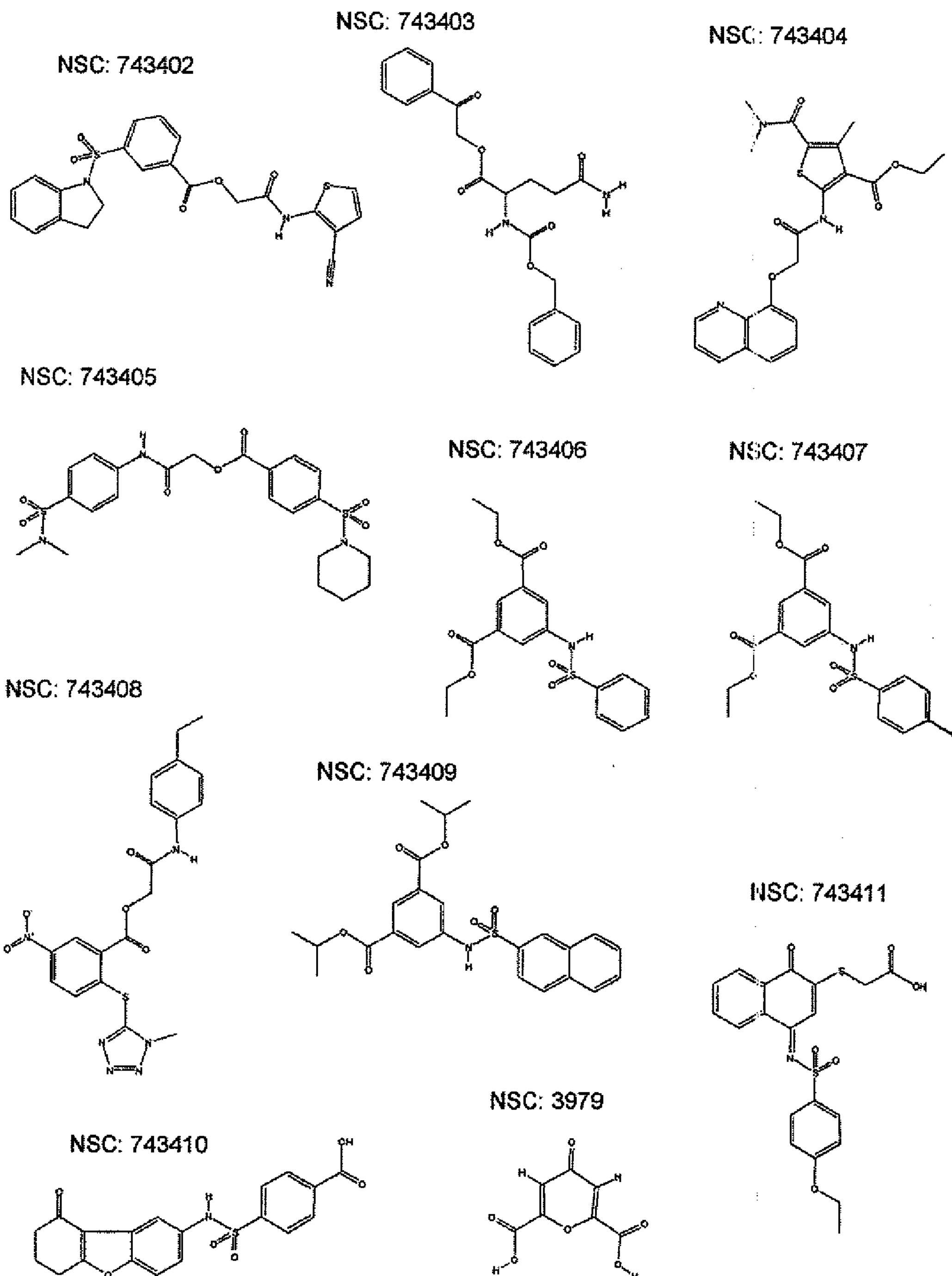
[0111] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0112] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0113] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

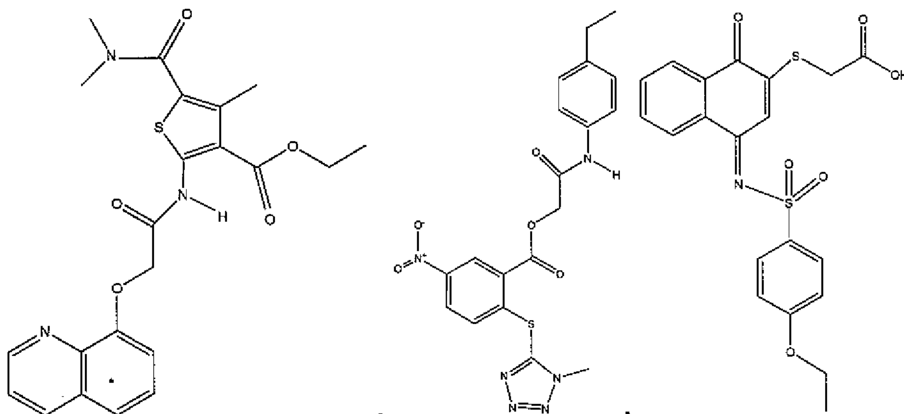
CLAIM(S):

1. A compound for inhibiting mTOR, wherein the compound has one of the following structures:

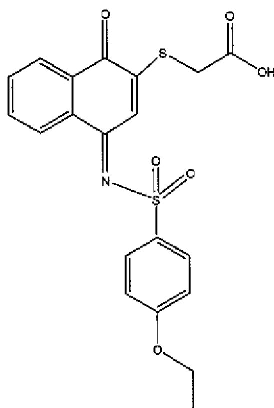


or a prodrug, salt, or solvate thereof.

2. The compound of claim 1, wherein the compound has one of the following structures:



3. The compound of claim 2, wherein the compound is:



4. The compound of any one of claims 1 to 3, wherein the compound inhibits Akt by inhibiting the binding of Akt's pleckstrin homology (PH) domain to a phosphoinositide.

5. The compound of any one of claims 1 to 3, wherein the compound activates AMP-activated protein kinase (AMPK).

6. The compound of any one of claims 1 to 5, wherein the compound inhibits Akt and activates AMPK.

7. The compound of any one of claims 1 to 6, wherein the compound treats or prevents development of cancer or prevents progression of premalignant lesions to cancer in an animal.

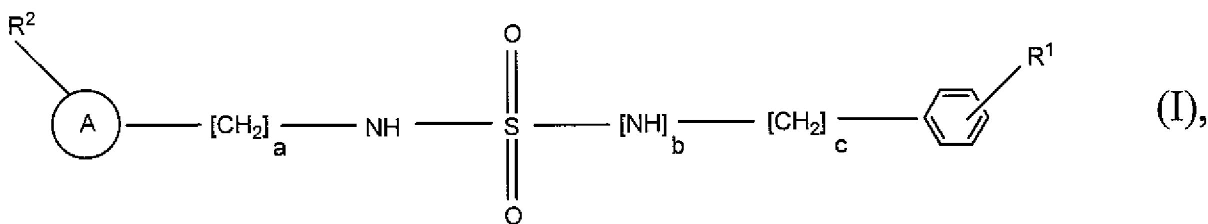
8. The compound of claim 7, wherein the cancer is selected from the group consisting of glioma, thyroid carcinoma, breast carcinoma, small-cell lung carcinoma, non-small-cell carcinoma, gastric carcinoma, colon carcinoma, gastrointestinal stromal tumor, pancreatic carcinoma, bile duct carcinoma, CNS carcinoma, ovarian carcinoma, endometrial carcinoma, prostate carcinoma, renal carcinoma, anaplastic large-cell lymphoma, leukemia, multiple myeloma, mesothelioma, and melanoma, and combinations thereof.

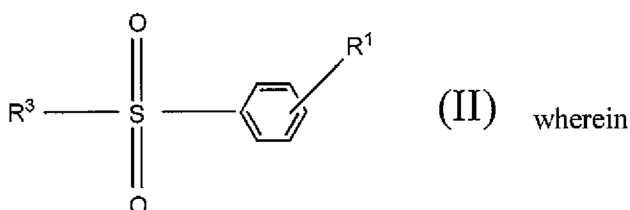
9. The compound of claim 8, wherein the cancer is selected from the group consisting of leukemia, non-small-cell carcinoma, breast carcinoma, colon carcinoma, CNS carcinoma, melanoma, ovarian carcinoma, renal carcinoma, and prostate carcinoma.

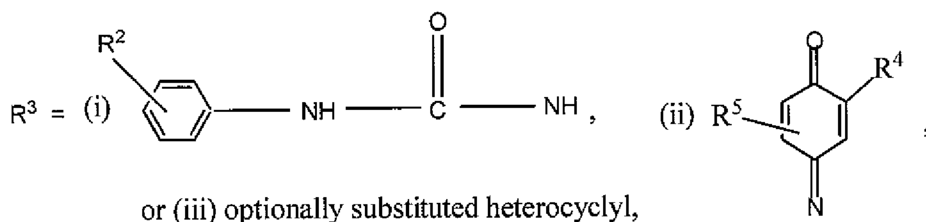
10. The compound of claim 9, wherein the cancer is a non-small-cell carcinoma.

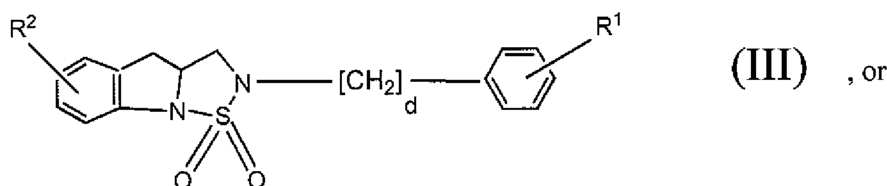
11. The compound of claim 10, wherein the non-small-cell carcinoma is characterized by a cell line selected from the group consisting of H1703, MB468, PC3, H460, and H157.

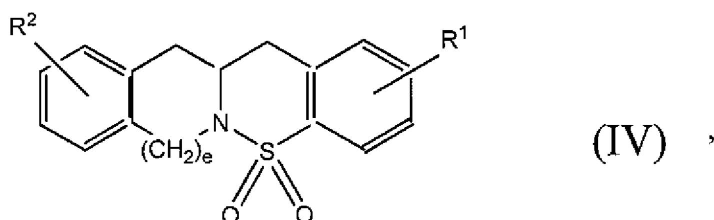
12. A compound for inhibiting mTOR, wherein the compound is of formula (I), (II), (III), or (IV):











wherein A is C_6-C_{20} aryl, C_6-C_{20} aryl C_1-C_6 alkyl C_6-C_{20} aryl, heteroaryl, or heteroaryl C_1-C_6 alkyl, optionally further substituted, at the aryl, alkyl, or at the heteroaryl moiety, with one or more substituents selected from the group consisting of C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and hydroxy C_1-C_6 alkyl;

R^1 is selected from the group consisting of C_1-C_6 alkyl, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and nitro;

R^2 is selected from the group consisting of hydrogen, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl;

R^4 is selected from the group consisting of carboxy C_1-C_6 alkyl, carboxy C_1-C_6 alkoxy, and carboxy C_1-C_6 alkylthio;

R^5 is hydrogen, C_6-C_{20} aryl which may be linked at one carbon atom or on two carbon atoms as fused, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl, which may be optionally substituted with a substituent selected from the group consisting of C_1-C_6 alkyl, halo, nitro, hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl; and

a, b, c, d, and e are independently 0 to 6;

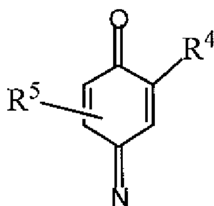
or a prodrug, salt, or solvate thereof.

13. The compound of claim 12, wherein the compound of formula (I) has a, b, and c as 0 or a, b, and c as 1.

14. The compound of claim 12, wherein the compound of formula (I) has a as 1 and b and c as 0 or a and c as 0 and b as 1.

15. The compound of claim 12, wherein the compound of formula (II) has a, b, and c as 0.

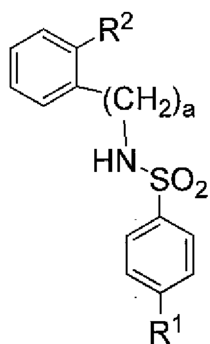
16. The compound of claim 12, wherein the compound of formula (II) has R^1 as ethoxy and R^3 as



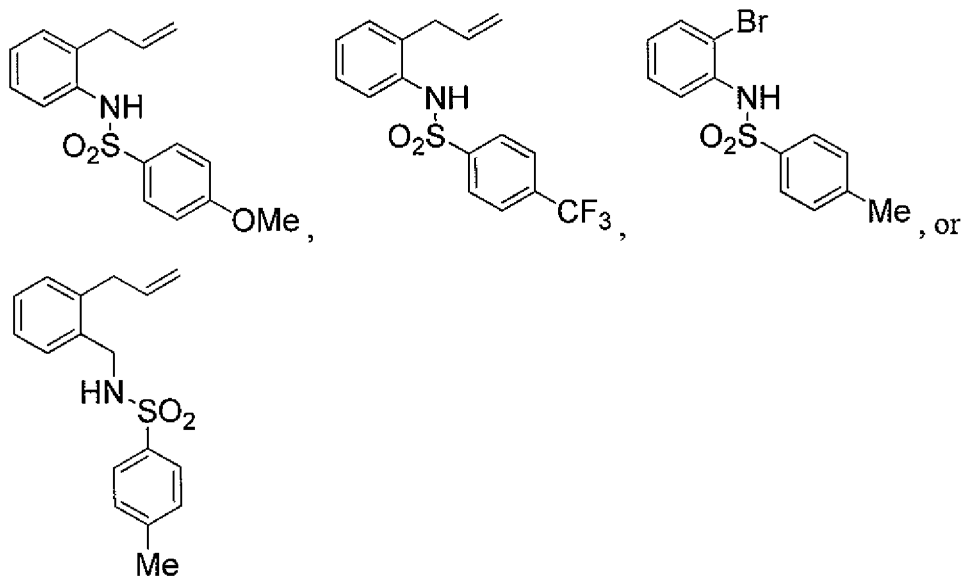
, or a prodrug, salt, or solvate thereof.

17. The compound of claim 16, wherein R^4 is carboxymethylthio and R^5 is benzo.

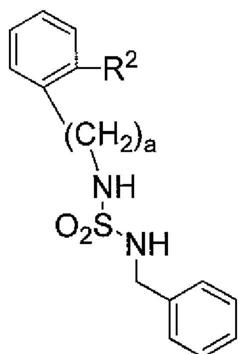
18. The compound of claim 12, wherein the compound of formula (I) has the structure



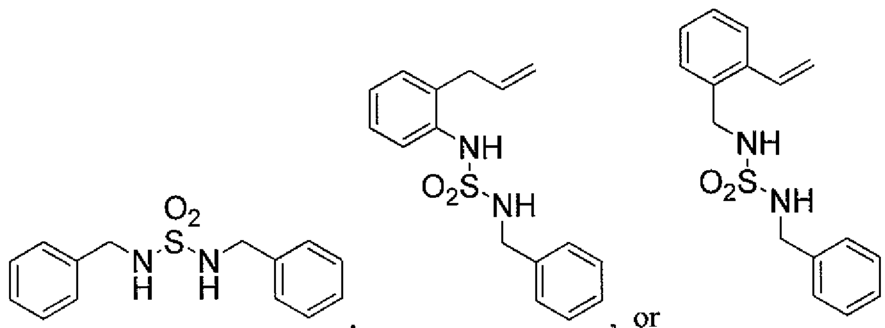
19. The compound of claim 18, wherein the compound is



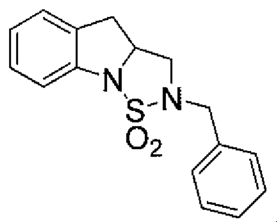
20. The compound of claim 12, wherein the compound of formula (I) has the structure



21. The compound of claim 20, wherein the compound is



22. The compound of claim 12, wherein the compound is



23. The compound of any one of claims 12 to 22, wherein the compound inhibits Akt by inhibiting the binding of Akt's pleckstrin homology (PH) domain to a phosphoinositide.

24. The compound of any one of claims 12 to 22, wherein the compound activates AMP-activated protein kinase (AMPK).

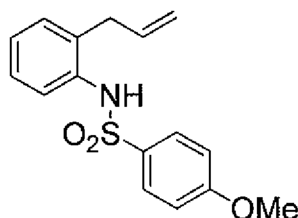
25. The compound of any one of claims 12 to 24, wherein the compound inhibits Akt and activates AMPK.

26. The compound of any one of claims 12 to 25, wherein the compound treats or prevents development of cancer or prevents progression of premalignant lesions to cancer in an animal.

27. The compound of claim 26, wherein the tumor is characterized by cell line A549 or H1703.

28. The compound of any one of claims 12 to 27, wherein the compound administered arrests the G2/M phase of the tumor cell cycle.

29. The compound of claim 28, wherein the compound is:



sulfonamide-2

30. The compound of claim 26, wherein the cancer is selected from the group consisting of glioma, thyroid carcinoma, breast carcinoma, small-cell lung carcinoma, non-small-cell carcinoma, gastric carcinoma, colon carcinoma, gastrointestinal stromal tumor, pancreatic carcinoma, bile duct carcinoma, CNS carcinoma, ovarian carcinoma, endometrial carcinoma, prostate carcinoma, renal carcinoma, anaplastic large-cell lymphoma, leukemia, multiple myeloma, mesothelioma, and melanoma, and combinations thereof.

31. The compound of claim 7 or 26, which is for administration in conjunction with another cancer therapy.

32. The compound of claim 31, wherein the another cancer therapy comprises chemotherapy, radiation therapy, or biological therapy.

33. The compound of claim 32, wherein the biological therapy involves administration of a protein.

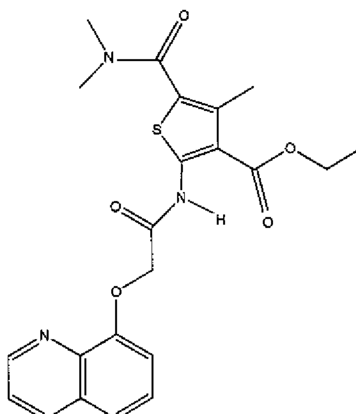
34. The compound of claim 33, wherein the protein is an antibody or recombinant protein.

35. The compound of claim 31, wherein the another cancer therapy comprises chemotherapy.

36. The compound of claim 35, wherein the another cancer therapy involves the administration of an agent selected from the group consisting of abarelix, aldesleukin, alemtuzumab, altretamine, amifostine, aminoglutethimide, anastrazole, arsenic trioxide, asparaginase, azacitidine, azathioprine, BCG vaccine, bevacizumab, bexarotene, bicalutamide, bleomycin sulfate, bortezomib, bromocriptine, busulfan, capecitabine,

carboplatin, carmustine, cetuximab, chlorambucil, chloroquine phosphate, cladribine, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, daunorubicin citrate liposomal, dexrazoxane, docetaxel, doxorubicin hydrochloride, doxorubicin hydrochloride liposomal, epirubicin hydrochloride, estramustine phosphate sodium, etoposide, estretinate, exemestane, floxuridine, fludarabine phosphate, fluorouracil, fluoxymesterone, flutamide, fulvestrant, gefitinib, gemcitabine hydrochloride, gemtuzumab ozogamicin, goserelin acetate, hydroxyurea, idarubicin hydrochloride, ifosfamide, imtinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan hydrochloride trihydrate, letrozole, leucovorin calcium, leuprolide acetate, levamisole hydrochloride, lomustine, lymphocyte immune anti-thymocyte globulin (equine), mechlorethamine hydrochloride, medoxyprogestone acetate, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone hydrochloride, nilutamide, oxaliplatin, paclitaxel, pegaspargase, pentostatin, plicamycin, porfimer sodium, procarbazine hydrochloride, streptozocin, tamoxifen citrate, temozolomide, teniposide, testolactone, testosterone propionate, thioguanine, thiotepa, topotecan hydrochloride, tretinoin, uracil mustard, valrubicin, vinblastine sulfate, vincristine sulfate, and vinorelbine.

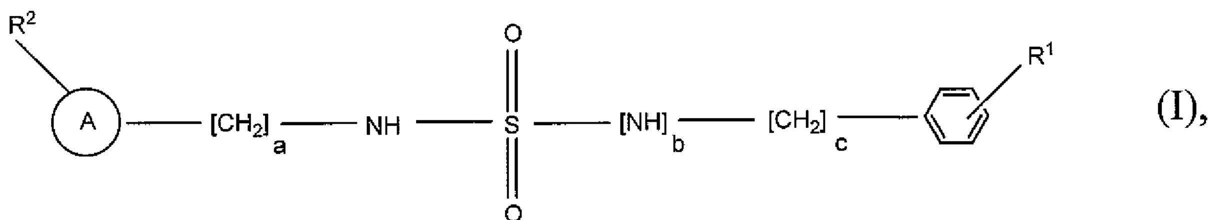
37. A compound for treating an animal for a disease or adverse condition that responds to inhibiting the activity of CSF1R receptor, wherein the compound is of the formula



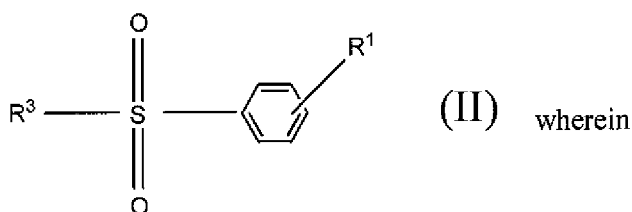
so that the disease or the adverse condition is treated.

38. The compound of claim 37, wherein the disease or adverse condition is chronic myelomonocytic leukemia, Alzheimer's disease, or brain injury.

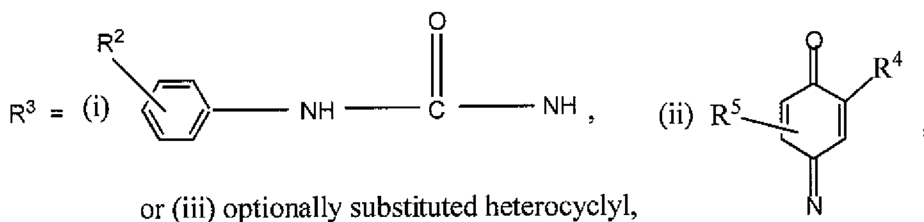
39. A compound of one of formulas (I)-(IV):



(I),

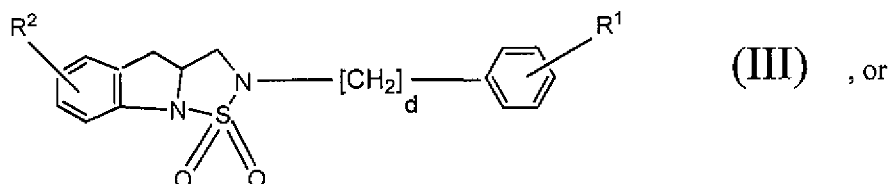


(II) wherein

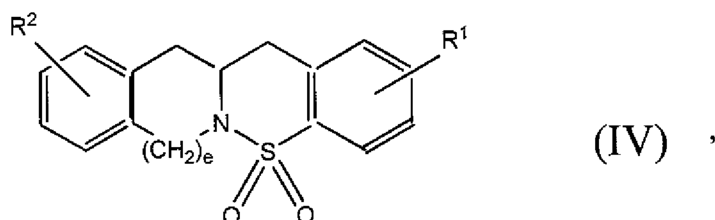


,

or (iii) optionally substituted heterocyclyl,



(III) , or



(IV) ,

wherein A is C_6-C_{20} aryl, C_6-C_{20} aryl C_1-C_6 alkyl C_6-C_{20} aryl, heteroaryl, or heteroaryl C_1-C_6 alkyl, optionally further substituted, at the aryl, alkyl, or at the heteroaryl moiety, with one or more substituents selected from the group consisting of C_2-C_6 alkenyl,

halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and hydroxy C_1-C_6 alkyl;

R^1 is selected from the group consisting of C_1-C_6 alkyl, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, and nitro;

R^2 is selected from the group consisting of hydrogen, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl;

R^4 is selected from the group consisting of carboxy C_1-C_6 alkyl, carboxy C_1-C_6 alkoxy, and carboxy C_1-C_6 alkylthio;

R^5 is hydrogen, C_6-C_{20} aryl which may be linked at one carbon atom or on two carbon atoms as fused, C_2-C_6 alkenyl, halo, monohalo C_1-C_6 alkyl, dihalo C_1-C_6 alkyl, trihalo C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, and heterocyclyl, which may be optionally substituted with a substituent selected from the group consisting of C_1-C_6 alkyl, halo, nitro, hydroxy, C_2-C_6 alkenyl, and C_1-C_6 alkoxy carbonyl amino C_1-C_6 alkyl; and

a, b, c, d, and e are independently 0 to 6;

or a prodrug, salt, or solvate thereof;

with the provisos that:

(a) in formula (I), when all of a, b, and c are 0 or 1 or when at least one of a, b, and c is 0 and at least one of the other is less than 2, and R^2 is alkenyl, then R^1 is not hydrogen, alkyl, halogen, alkoxy, nitro, or trifluoromethoxy;

(b) in formula (II), when R^3 is (i) and R^2 is alkenyl, then R^1 is not alkyl; when R^3 is (ii) and R^1 is ethoxy, R^4 is carboxy alkyl thio, R^5 is not benzo; when R^3 is (iii) optionally substituted heterocyclyl and R^1 is alkyl, then the substituted heterocyclyl is not an indole substituted with alkoxycarbonyl amino alkyl;

(c) in formula (III), when R^2 is hydrogen and d is 1, then R^1 is not hydrogen; and when R^2 is hydrogen and d is 0, then R^1 is not alkoxy; and

(d) in formula (IV), when R^2 is hydrogen and e is 0, then R^1 is not alkyl or alkoxy; and when R^2 is hydrogen and e is 1, then R^1 is not alkyl.

40. A pharmaceutical composition comprising a compound, prodrug, salt, or solvate of claim 39 and a pharmaceutically acceptable carrier.

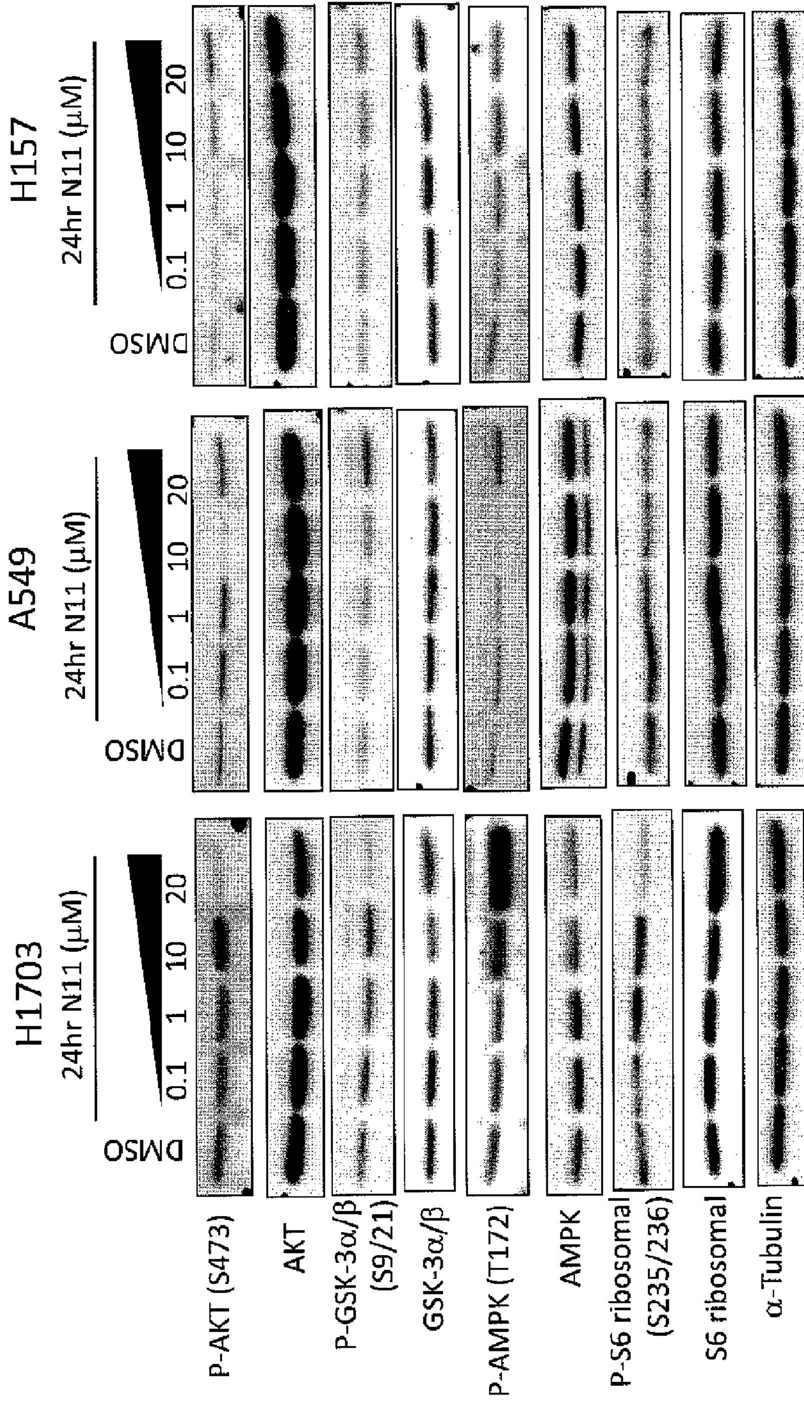


FIG. 1

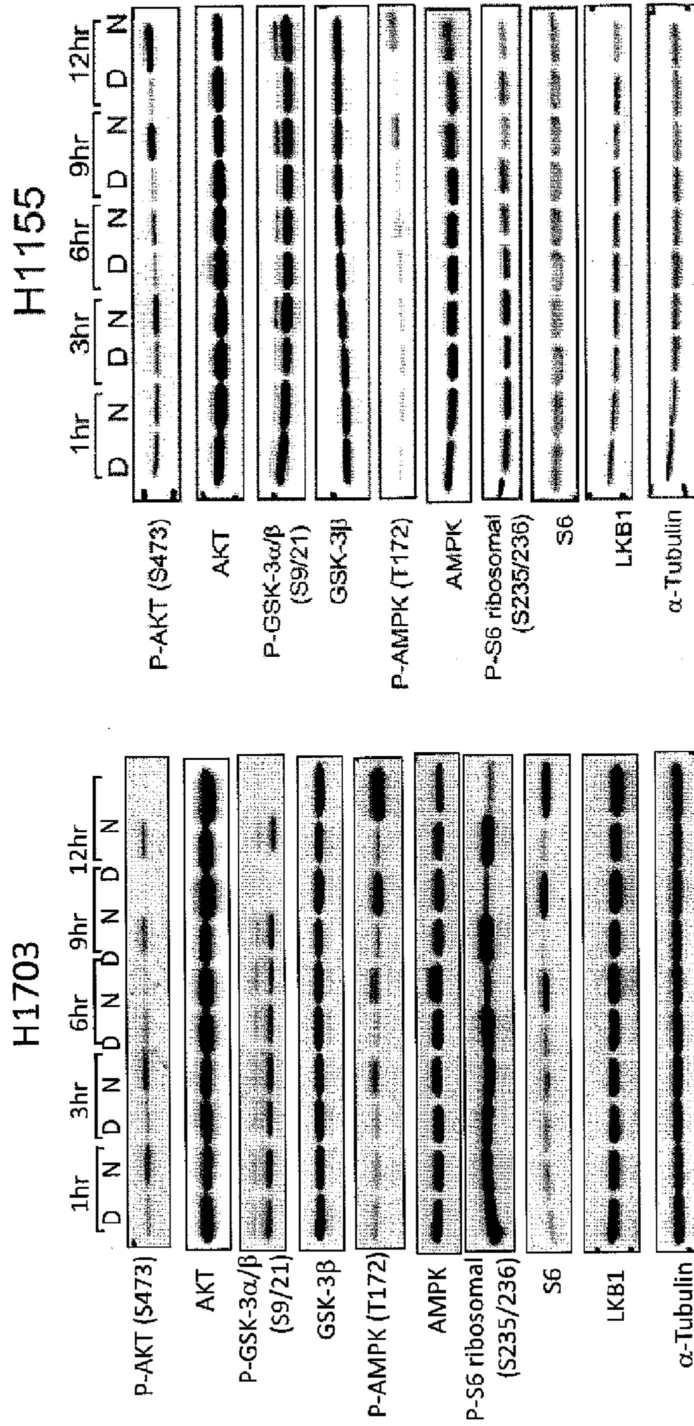


FIG. 2

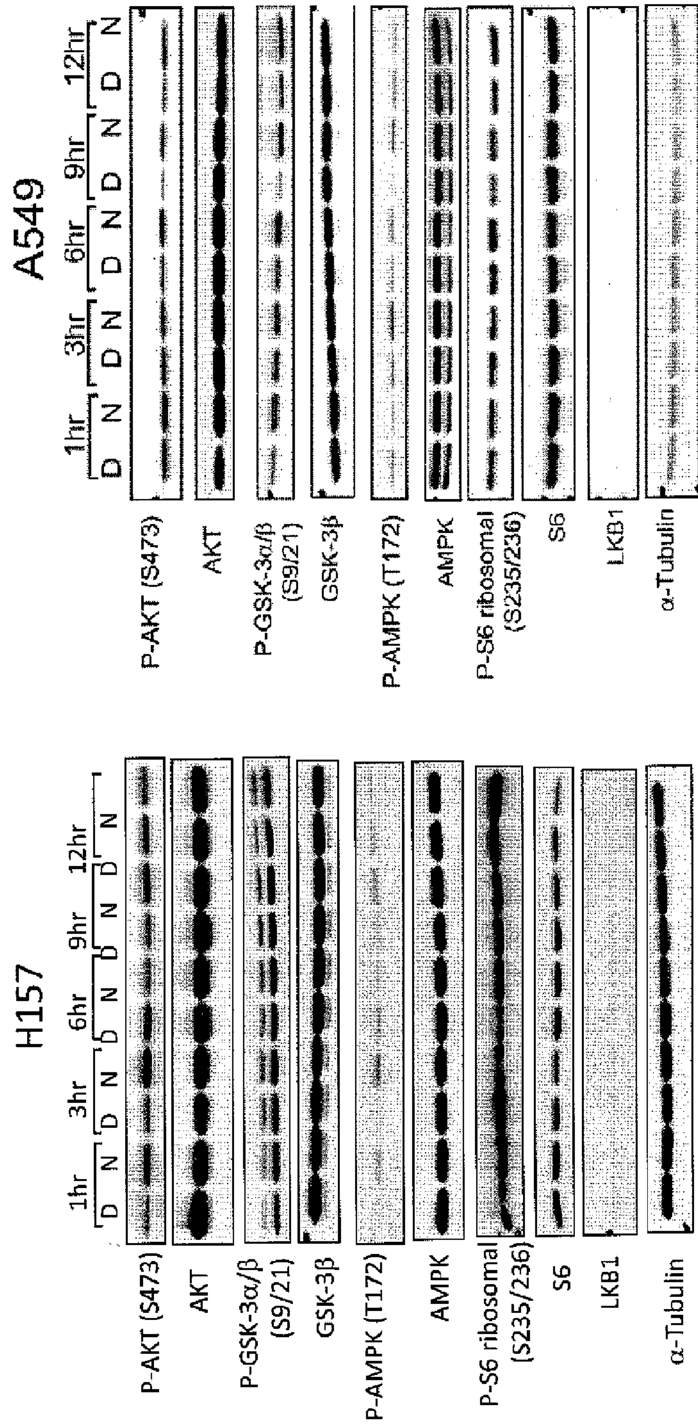


FIG. 3

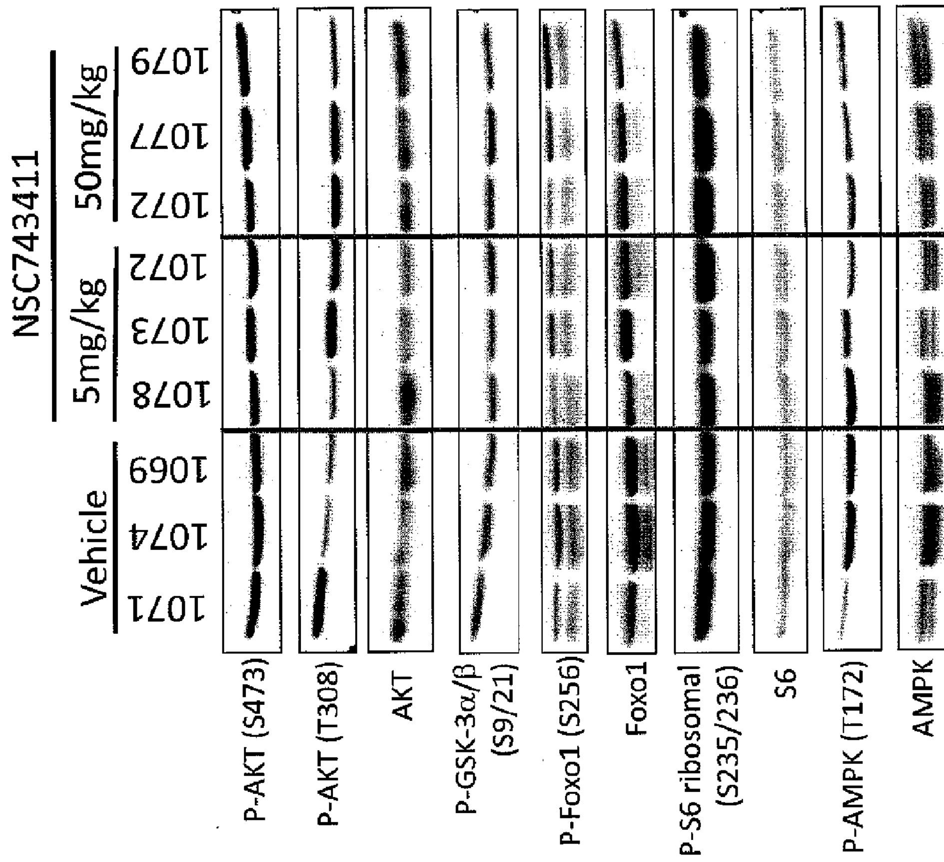


FIG. 4

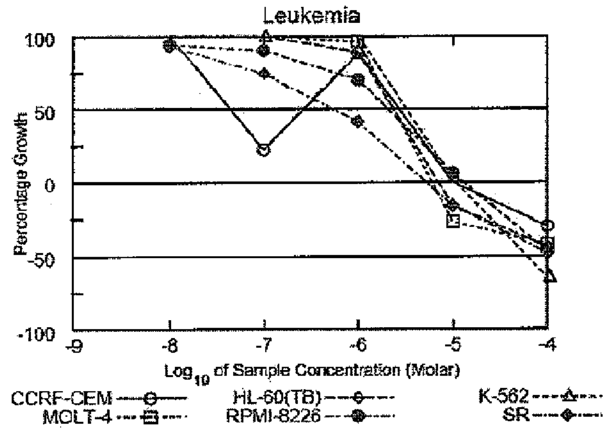


FIG. 5A

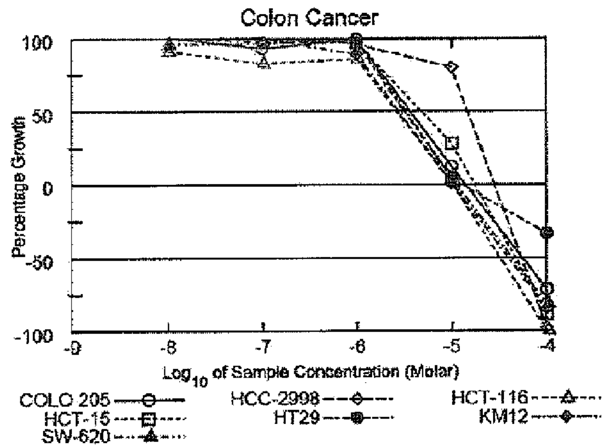


FIG. 5B

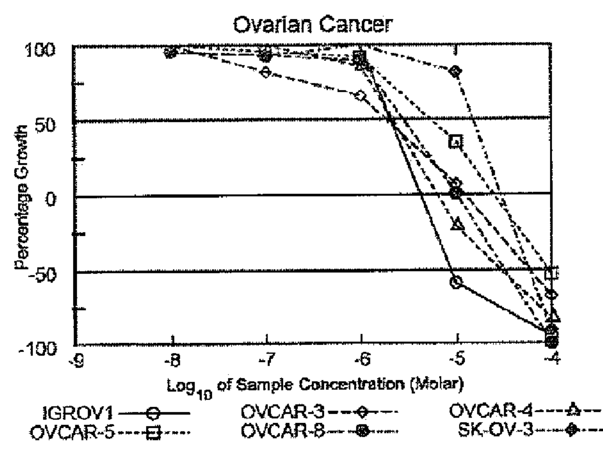


FIG. 5C

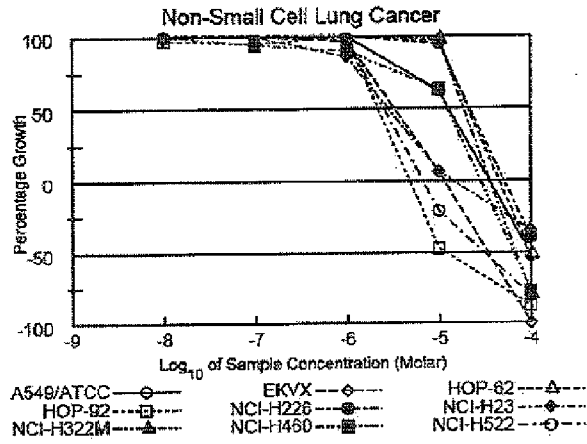


FIG. 5D

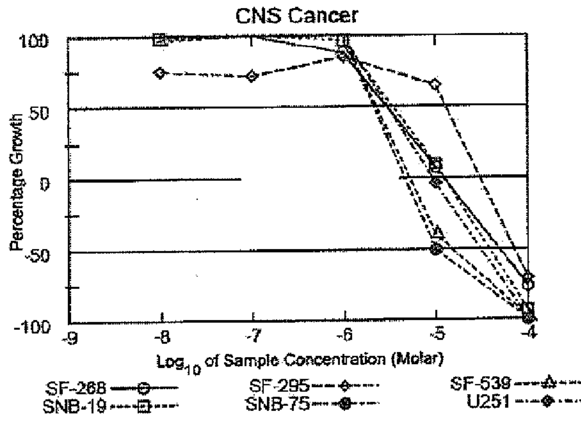


FIG. 5E

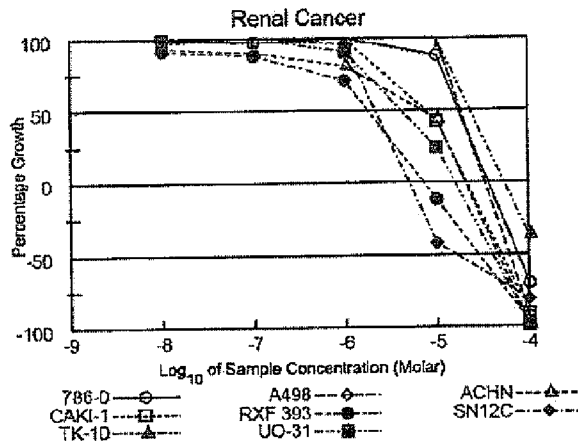


FIG. 5F

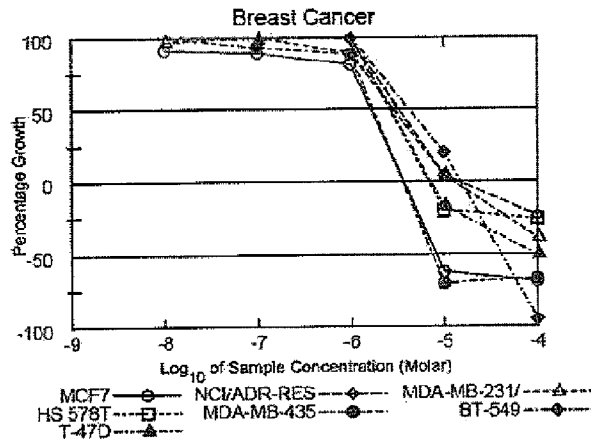


FIG. 5G

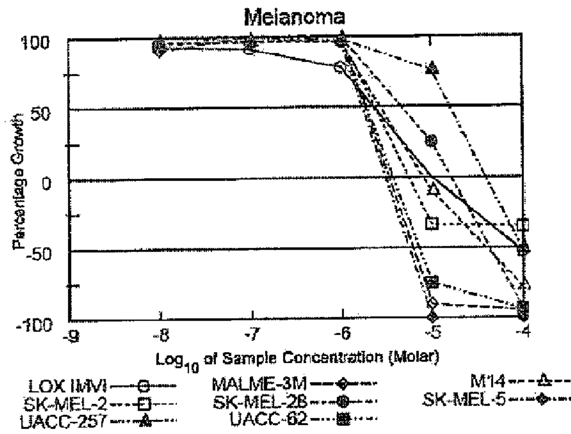


FIG. 5H

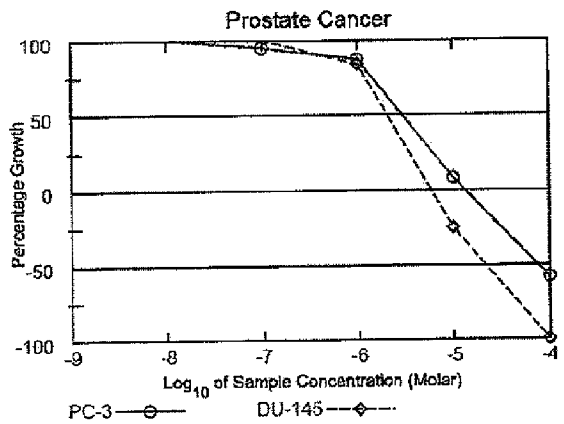


FIG. 5I

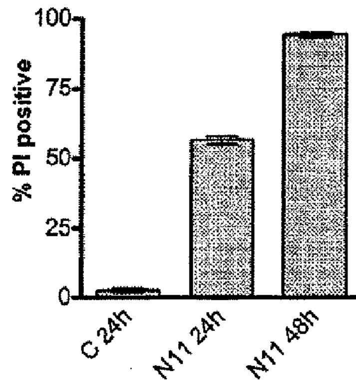


FIG. 6A

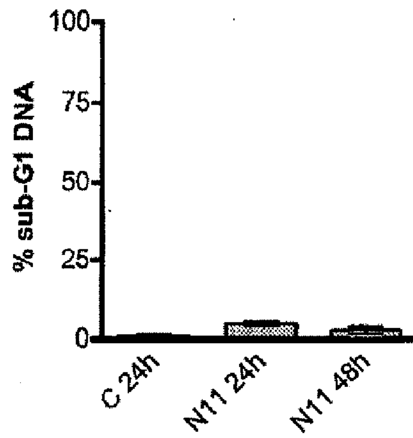


FIG. 6B

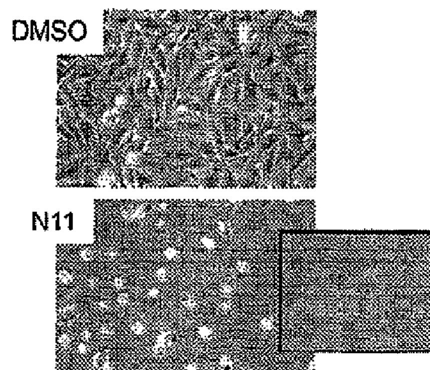


FIG. 6C

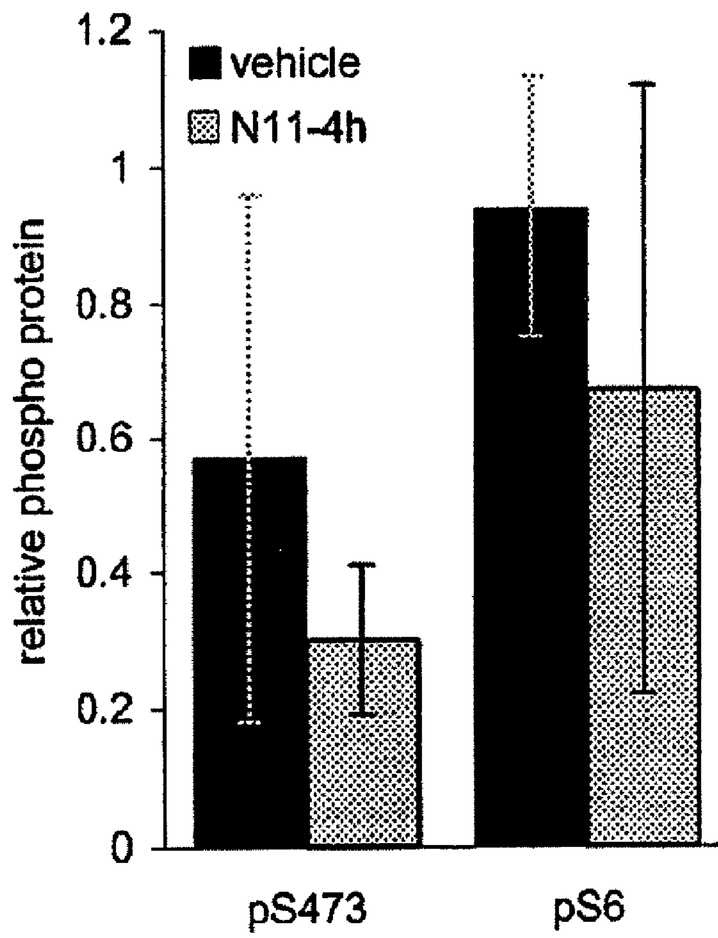


FIG. 7

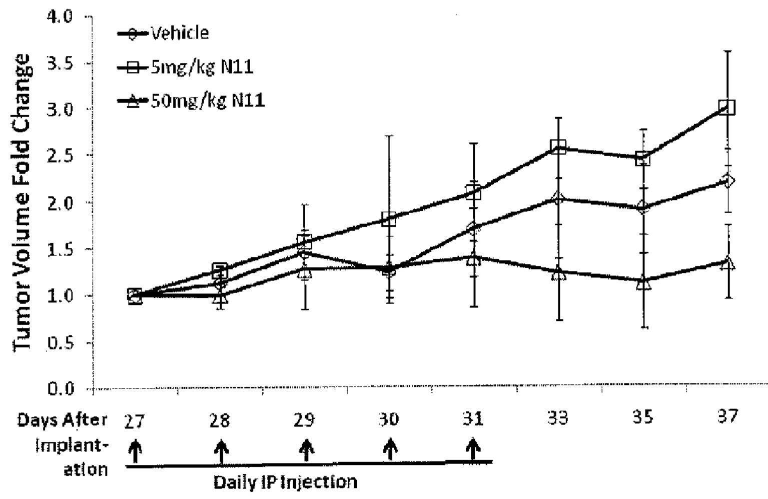


FIG. 8

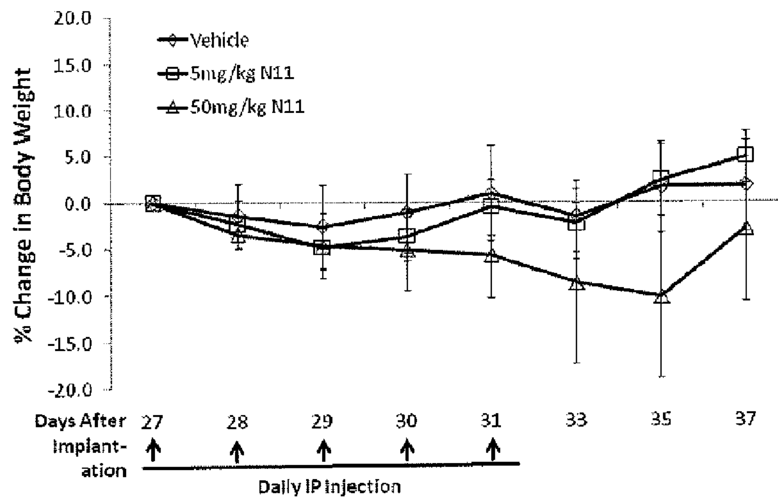
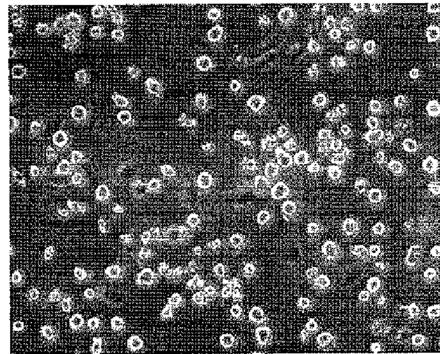


FIG. 9

FIG. 10A

FIG. 10B



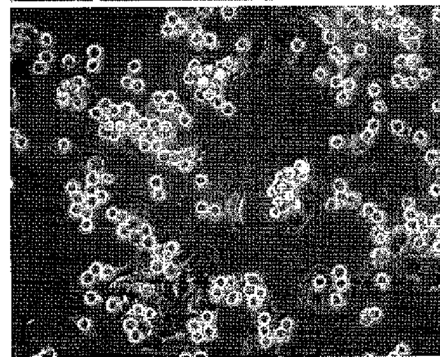


FIG. 10C

FIG. 10D

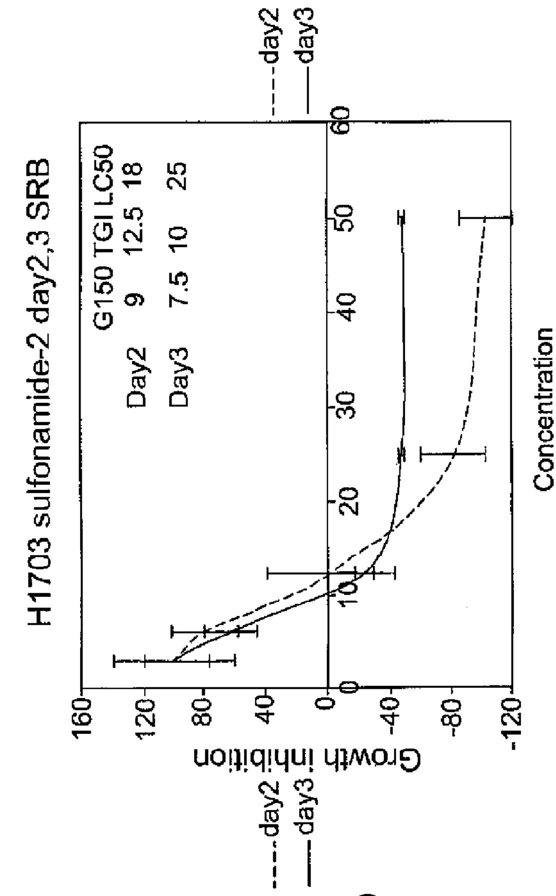


FIG. 11B

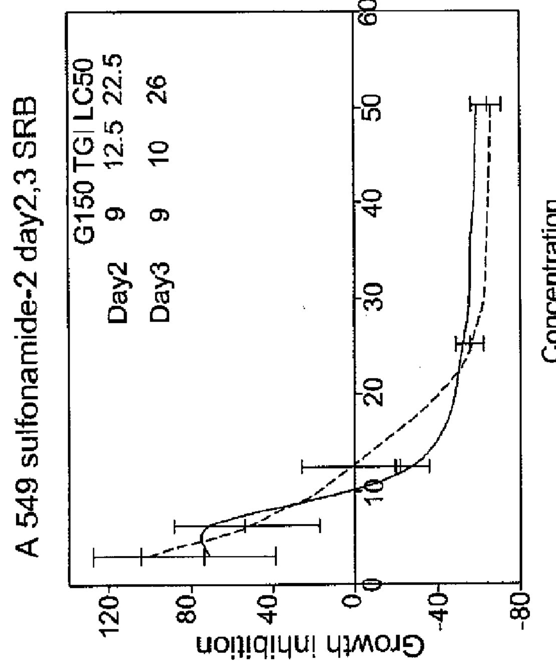


FIG. 11A

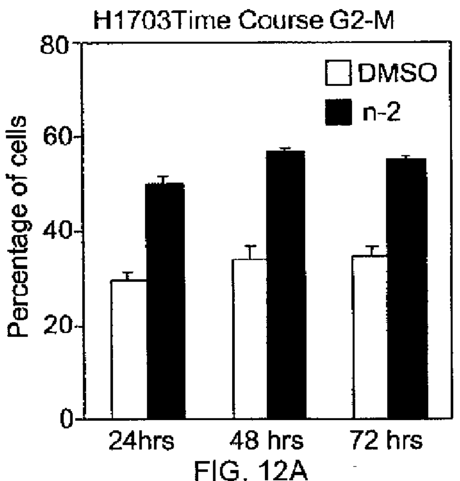


FIG. 12A

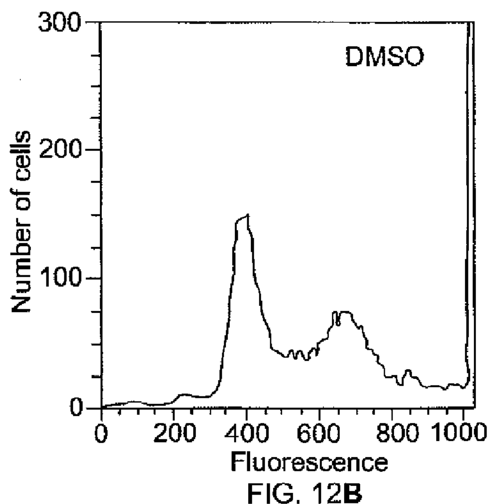


FIG. 12B

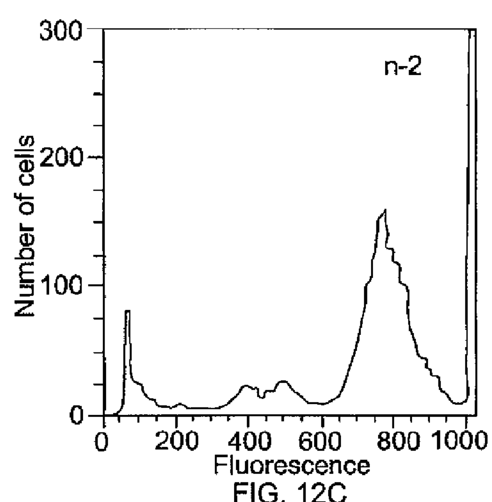


FIG. 12C

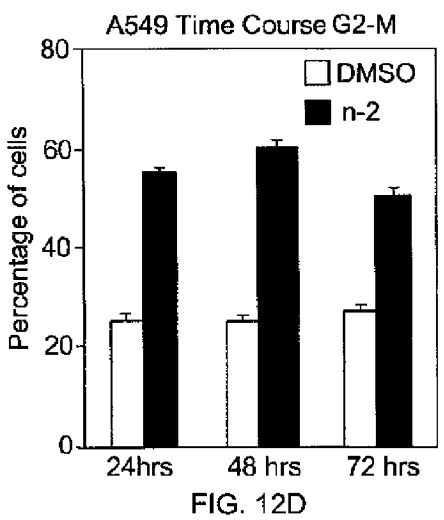


FIG. 12D

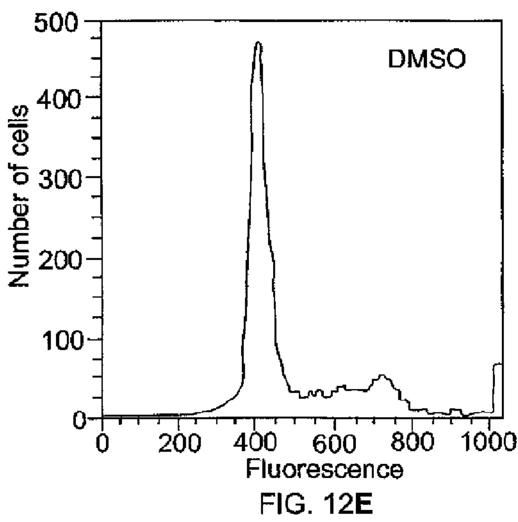


FIG. 12E

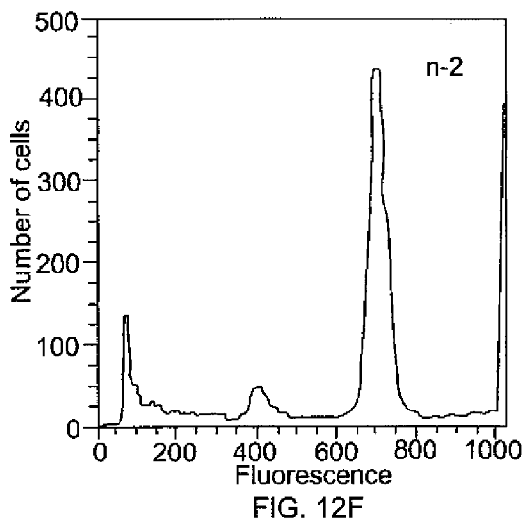


FIG. 12F

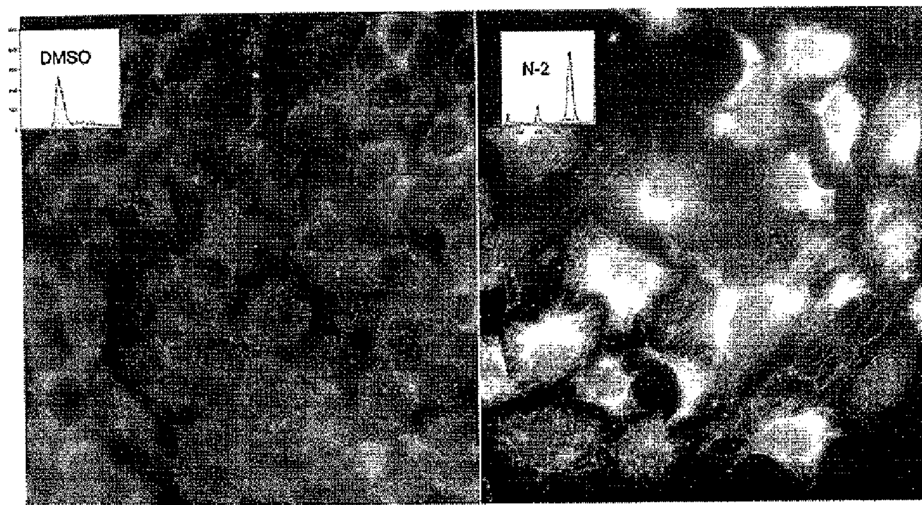


FIG. 13A FIG. 13B

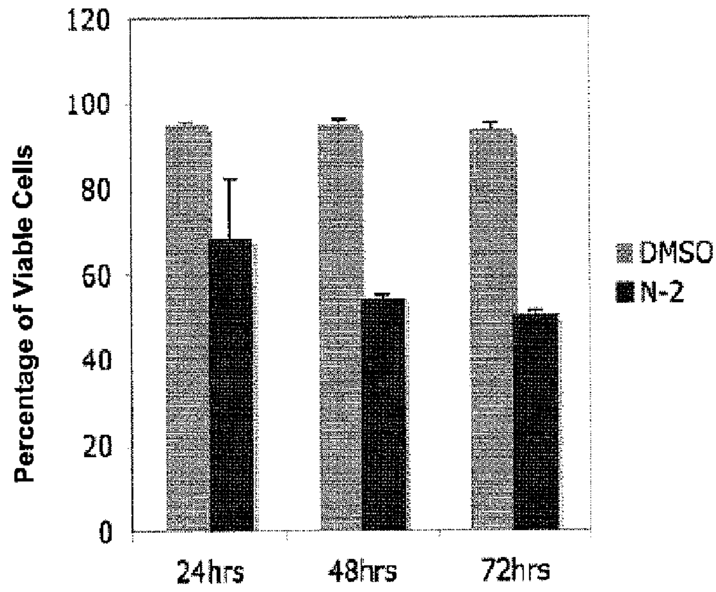


FIG. 14

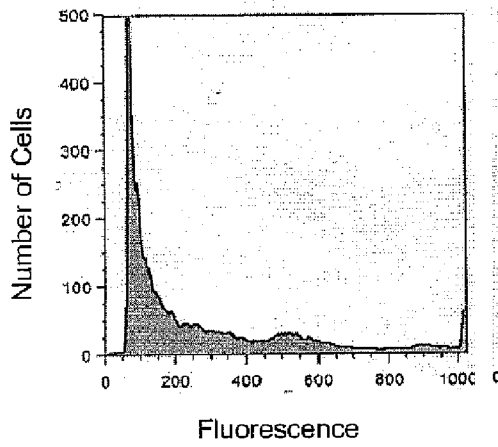


FIG. 15A

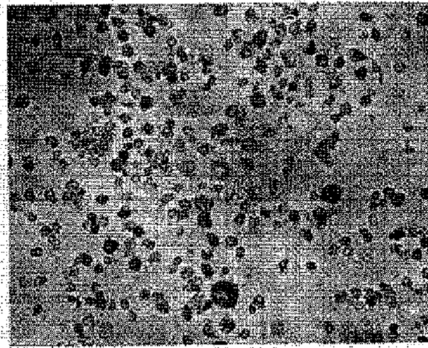


FIG. 15B

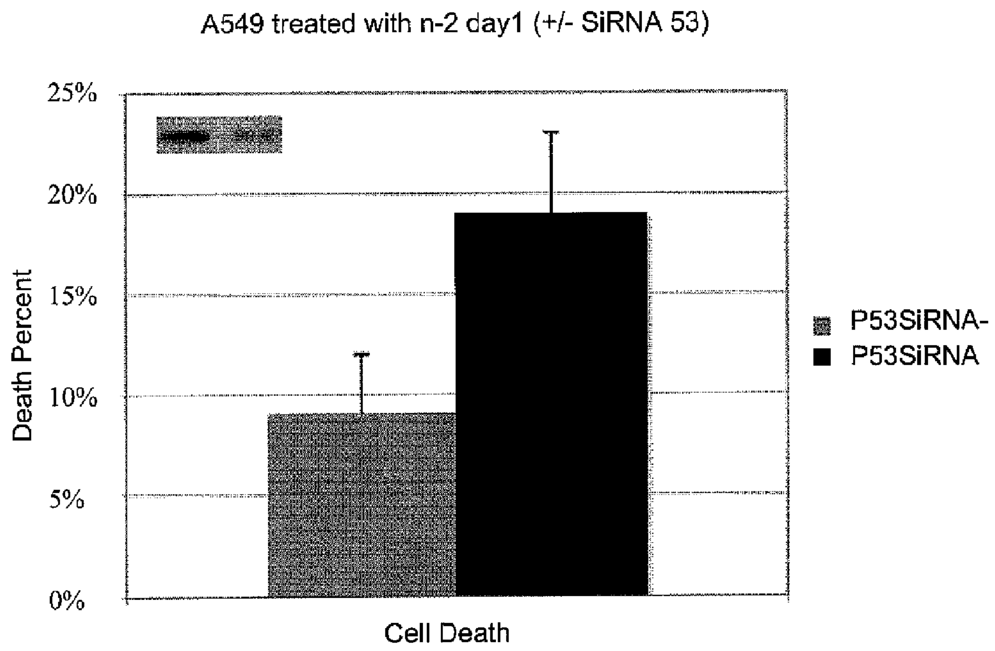


FIG. 16