(12) STANDARD PATENT (11) Application No. **AU 2003270087 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Akt inhibitors, pharmaceutical compositions, and uses thereof

(51) International Patent Classification(s)

A61K 31/683 (2006.01)	***A61P 31/04*** (2006.01)
A61P 9/00 (2006.01)	***A61P 31/12*** (2006.01)
A61P 11/00 (2006.01)	***A61P 31/14*** (2006.01)
A61P 11/08 (2006.01)	***A61P 33/00*** (2006.01)
A61P 15/00 (2006.01)	***A61P 35/00*** (2006.01)
A61P 17/00 (2006.01)	***A61P 35/02*** (2006.01)
A61P 19/02 (2006.01)	***A61P 43/00*** (2006.01)
A61P 25/00 (2006.01)	***C07C 43/196*** (2006.01)
A61P 29/00 (2006.01)	***C07F 9/117*** (2006.01)

(21) Application No: **2003270087** (22) Date of Filing: **2003.09.03**

(87) WIPO No: **WO04/022569**

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/407,239	**2002.09.03**	**US**

(43) Publication Date: **2004.03.29**
(43) Publication Journal Date: **2004.05.13**
(44) Accepted Journal Date: **2009.04.23**

(71) Applicant(s)
The Government of the United States of America, as represented by the Secretary, Department of Health & Human Services;Georgetown University

(72) Inventor(s)
Brognard, John;Dennis, Phillip;Kozikowski, Alan P.;Sun, Haiying

(74) Agent / Attorney
Fisher Adams Kelly, 29/12 Creek Street, Brisbane, QLD, 4000

(56) Related Art
WO 2000/000206
Hu et al. Tetrahedron Letters (2000) 41(39): 7415-7418
US 5227508

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 March 2004 (18.03.2004)

PCT

(10) International Publication Number
WO 2004/022569 A1

(51) International Patent Classification[7]: C07F 9/117, C07C 59/13, 59/68, A61K 31/683, 31/185, A61P 35/00

(21) International Application Number:
PCT/US2003/027607

(22) International Filing Date:
3 September 2003 (03.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/407,239 3 September 2002 (03.09.2002) US

(71) Applicants *(for all designated States except US)*: **GEORGETOWN UNIVERSITY** [US/US]; 37th & O Streets, N.W., Washington, DC 20057 (US). **THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as representedby THE SECRETARY, DEPARTMENT OF HEALT H ANDHUMANSERVICES** [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KOZIKOWSKI, Alan, P.** [US/US]; 1600 Oak St., N, Apt 1022, Arlington, VA 22209 (US). **DENNIS, Phillip** [US/US]; 2327 Daniels, Rd., Ellicott City, MD 21043 (US). **SUN, Haiying** [CN/US]; 1515 Jones Dr., Apt 14, Ann Arbor, MI 48105 (US). **BROGNARD, John** [US/US]; 821 Skysail Ave., Carlsbad, CA 92009 (US).

(74) Agents: **PILLAI, Xavier** et al.; Leydig, Voit & Mayer, LTD., Two Prudential Plaza, Suite 4900, 180 North Stetson, Chicago, IL 60601-6780 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

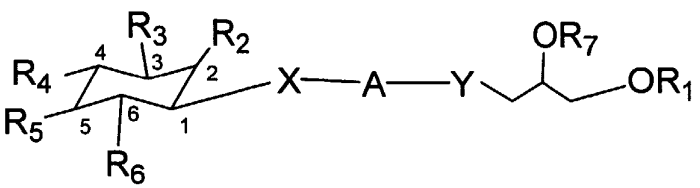
Published:
— *with international search report*

(48) Date of publication of this corrected version:
10 June 2004

(15) Information about Correction:
see PCT Gazette No. 24/2004 of 10 June 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AKT INHIBITORS, PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF



(I)

(57) Abstract: Disclosed are inhibitors of the serine/threonine kinase Akt, pharmaceutical compositions comprising such inhibitors, and a method of preventing or treating a disease or condition in an animal by the use of such inhibitors. The Akt inhibitors have the formula (I) wherein X and Y are independently selected from the group consisting of O, CF_2, CH_2, and CHF; wherein A is independently selected from the group consisting of P(O)OH, CH_2000H, and $CH(COOH)_2$; R_2 is selected from the group consisting of H, OH, isosteres of OH, C_1-C_{25} alkyloxy, C_6-C_{10} aryloxy, C_3-C_8 cycloalkyloxy, C_3-C_8 cycloalkyl C_1-C_6 alkoxy, C_2-C_{22} alkenyloxy, C_3-C_8 cycloalkenyloxy, C_7-C_{32} aralkyloxy, C_7-C_{32} alkylaryloxy, C_9-C_{32} aralkenyloxy, and C_9-C_{32} alkenylaryloxy; R_3-R_6 are independently selected from the group consisting of H, OH, isosteres of OH; and R_1 and R_7 are independently selected from the group consisting of C_1-C_{25} alkyl, C_6-C_{10} aryl, C_3-C_8 cycloalkyl, C_2-C_{22} alkenyl, C_3-C_8 cycloalkenyl, C_7-C_{32} aralkyl, C_7-C_{32} alkylaryl, C_9-C_{32} aralkenyl, and C_9-C_{32} alkenylaryl; with the provisos that (i) when X is O, Y is O or CH_2, and R_3 is H, at least one of R_2 and R_4-R_6 is not OH; (ii) when A is CH_2C00H or $CH(COOH)_2$, X and Y cannot be simultaneously O; and (iii) all of R_2-R_6 are not simultaneously H. The inhibitors can be in the form of a salt also.

WO 2004/022569 A1

AKT INHIBITORS, PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 60/407,239, filed September 3, 2002, the disclosure of which is incorporated by reference.

FIELD OF THE INVENTION

[0002] This invention pertains to inhibitors of the serine/threonine kinase Akt, pharmaceutical compositions, and a method of preventing or treating of diseases activated by Akt.

BACKGROUND OF THE INVENTION

[0003] Akt (or protein kinase B (PKB)) is a well-characterized serine/threonine kinase that promotes cellular survival. Akt is activated in response to many different growth factors, including IGF-I, EGF, bFGF, insulin, interleukin-3, interleukin-6, heregulin, and VEGF (1). Akt is the cellular homologue of the product of the *v-akt* oncogene (2-4) and has 3 isoforms, Akt 1, 2, and 3 (or PKB α, β, and γ). Activation of all three isoforms is similar in that phosphorylation of two sites, one in the activation domain and one in the C-terminal hydrophobic motif, are necessary for full activity.

[0004] For Akt 1, phosphorylation of T308 in the activation domain by PDK1 is dependent on the products of phosphatidylinositol (PI) 3-kinase (PI3-K), phosphatidylinositol 3,4 bisphosphate (PIP_2) and phosphatidylinositol 3,4,5 trisphosphate (PIP_3). Cellular levels of PIP_2 and PIP_3 are controlled by the tumor suppressor, dual-phosphatase PTEN, which dephosphorylates PIP_2 and PIP_3 at the 3'-position. The mechanism of S473 phosphorylation is less clear. Kinases potentially responsible for S473 phosphorylation include PDK1 (5), ILK or an ILK- associated kinase (6, 7), Akt itself (8) or an as yet uncharacterized PDK2. Akt activation may also be achieved through PI3-K independent means, by phosphorylation of Akt by kinases such as PKA (9) or CAM-KK (10). Once activated, Akt exerts anti-apoptotic effects through phosphorylation of substrates that directly regulate the apoptotic machinery such as Bad (11, 12) or caspase 9 (13), or phosphorylation of substrates that indirectly inhibit apoptosis such the human telomerase reverse transcriptase subunit (hTERT) (14), forkhead transcription family members (15, 16), or IκB kinases (17, 18).

[0005] Functionally, Akt promotes survival *in vitro* when cells are exposed to different apoptotic stimuli such as GF withdrawal, UV irradiation, matrix detachment, cell cycle discordance, DNA damage, and administration of anti-Fas antibody, TGF-β, glutamate, or

bile acids (19-33). *In vivo*, activation of the PI3K/Akt pathway contributes to tumorigenesis in many types of tissues, including breast, ovarian, brain, prostate, and lymph tissues (34). It has been shown that Akt is constitutively active in over 90% of NSCLC cell lines and contributes to both chemotherapeutic resistance and radiation resistance (35). In addition, it has been shown that Akt is constitutively active in many breast cancer cell lines, and serves a similar function in promotion of cellular survival and chemotherapeutic resistance (36).

[0006] The foregoing shows that inhibitors of Akt would be desirable for preventing or treating a number of diseases, especially diseases such as cancer.

[0007] The advantages of the invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

BRIEF SUMMARY OF THE INVENTION

[0008] The invention provides compounds which are inhibitors of the Akt, pharmaceutical compositions comprising such an inhibitor and a pharmaceutically acceptable carrier, and a method of preventing or treating diseases by the use of such inhibitors. The inhibitors include phosphoinositol ether lipid analogues as well as bioisosteres thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Figure 1A depicts the formulas of some of the Akt inhibitors.

[0010] Figure 1B depicts the formulas of some other Akt inhibitors.

[0011] Figure 1C depicts the formulas of yet other Akt inhibitors.

[0012] Figure 1D depicts some of the immunoblots of the Akt inhibitors on S473 phosphorylation and total Akt levels.

[0013] Figure 1E depicts the effect of some of the Akt inhibitors on Akt kinase activity.

[0014] Figure 2A depicts the dose response curve for some of the Akt inhibitors.

[0015] Figure 2B depicts the dose response curves for some of the inhibitors on Akt phosphorylation.

[0016] Figure 3A depicts selectivity data for some of the Akt inhibitors on H1703 cells.

[0017] Figure 3B depicts selectivity data for some of the Akt inhibitors on H157 cells.

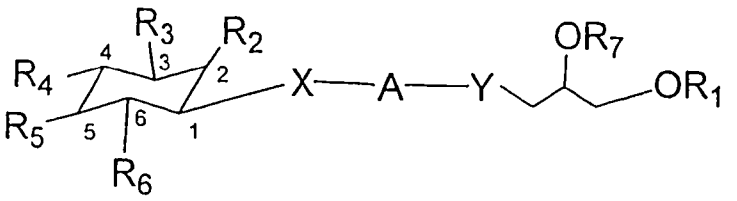
[0018] Figure 3C depicts selectivity data for some of the Akt inhibitors (SH 23-25) on H1703 cells.

[0019] Figure 3D depicts selectivity data for some of the Akt inhibitors on MB468 cells.

[0020] Figure 4 depicts the increase of apoptosis by Akt inhibitors on cells with high levels of Akt activity.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The present invention provides a compound of the formula I:



(I)

or a pharmaceutically acceptable salt thereof;

wherein X and Y are independently selected from the group consisting of O, CF_2, CH_2, and CHF;

A is independently selected from the group consisting of P(O)OH, CHCOOH, and $C(COOH)_2$;

R_2 is selected from the group consisting of H, OH, isosteres of OH, C_1-C_{25} alkyloxy, C_6-C_{10} aryloxy, C_3-C_8 cycloalkyloxy, C_3-C_8 cycloalkyl C_1-C_6 alkoxy, C_2-C_{22} alkenyloxy, C_3-C_8 cycloalkenyloxy, C_7-C_{32} aralkyloxy, C_7-C_{32} alkylaryloxy, C_9-C_{32} aralkenyloxy, and C_9-C_{32} alkenylaryloxy;

R_3-R_6 are independently selected from the group consisting of H, OH, isosteres of OH; and

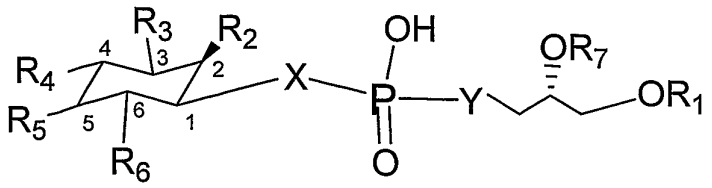
R_1 and R_7 are independently selected from the group consisting of C_1-C_{25} alkyl, C_6-C_{10} aryl, C_3-C_8 cycloalkyl, C_2-C_{22} alkenyl, C_3-C_8 cycloalkenyl, C_7-C_{32} aralkyl, C_7-C_{32} alkylaryl, C_8-C_{32} aralkenyl, and C_8-C_{32} alkenylaryl;

with the provisos that (i) when X is O, Y is O or CH_2, and R_3 is H, at least one of R_2 and R_4-R_6 is not OH; (ii) when A is CHCOOH, and $C(COOH)_2$, X and Y cannot be simultaneously O; and (iii) all of R_2-R_6 are not simultaneously H.

[0022] The alkyl and alkenyl portions of R_1-R_7 can be branched, or preferably linear. The aryl portion of R_1-R_7 can have one or more aromatic rings of 6-14 carbon atoms, for example, phenyl, naphthyl, or anthracyl rings. Isosteres of OH include F, Cl, SH, and the like.

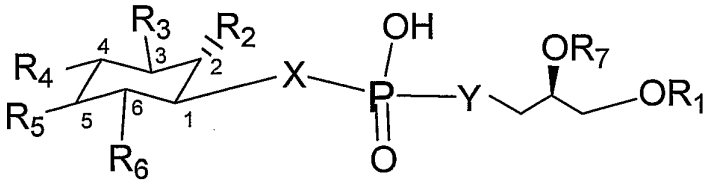
[0023] In a preferred embodiment, A is P(O)OH. In a further preferred embodiment, where A is P(O)OH, both X and Y are O.

[0024] The stereochemistry of attachment to the respective carbon atoms of R_2 and OR_7 can be in any suitable form, e.g., each can be *R*, *S*, or a mixture of *R* and *S* forms. Thus, for example, the compound of the present invention can have the formula Ia:



(Ia)

or the formula Ib:



(Ib),

the formula Ia being more preferred.

[0025] In some embodiments, compounds of the present invention, particularly those of the formula Ia and Ib, have as R_1 a C_1-C_{25} alkyl, preferably a C_{10}-C_{25} alkyl, and more preferably a C_{15}-C_{20} alkyl. Thus, for example, a particular R_1 is a C_{18} alkyl, e.g., n-$C_{18}H_{37}$. In certain embodiments, the compounds of the present invention have as R_7 a C_1-C_{25} alkyl, preferably a C_1-C_{15} alkyl, more preferably a C_1-C_5 alkyl. Thus, for example, a particular R_7 is methyl. In particularly preferred embodiments, R_1 is a C_{18} alkyl (e.g., n-$C_{18}H_{37}$) and R_7 is methyl.

[0026] In certain embodiments, compounds of the present invention, particularly those of the formula Ia and Ib, have as R_2 a C_1-C_{25} alkyloxy, preferably a C_1-C_{15} alkyloxy, more preferably a C_1-C_5 alkyloxy. A particular R_2 is methoxy. In certain other embodiments, R_2 is C_7-C_{32} aralkyloxy, and in some other embodiments, R_2 is C_3-C_8 cycloalkyloxy, or C_3-C_8 cycloalkyl C_1-C_6 alkoxy, e.g., cyclohexylmethyloxy.

[0027] In embodiments of the present invention, at least one of R_2, R_3, R_4, R_5, or R_6 is H, for example, R_2 and R_3 are H, R_3 and R_4 are H, or R_5 and R_6 are H.

[0028] In a preferred embodiment, A is P(O)OH, both X and Y are O, R_1 is $C_{18}H_{37}$, and R_7 is methyl. For example, in embodiments of the present invention, A is P(O)OH, both X and Y are O, R_1 is $C_{18}H_{37}$, and R_7 is methyl, and (i) R_2 is methoxy, R_3 is H, and R_4-R_6 are OH; (ii) R_2-R_3 are H and R_4-R_6 are OH; (iii) R_2-R_3 and R_5-R_6 are OH and R_4 is H; (iv) R_2 is i-butyl, R_3 is H, and R_4-R_6 are OH; (v) R_2 is cyclohexylmethoxy, R_3 is H, and R_4-R_6 are OH; (vi) R_2-R_3 and R_6 are OH and R_4-R_5 are H; (vii) R_2-R_4 and R_6 are OH and R_5 is H; or

(viii) R_2, R_4, and R_6 are OH and R_3 and R_5 are H. Some of the compounds of the present invention are shown in Figures 1A-1C.

[0029] The compounds of the present invention may be in the form of a pharmaceutically acceptable salt, for example, a salt of an alkali metal (e.g., sodium or potassium), alkaline earth metal (e.g., calcium), or ammonium of salt.

[0030] The present invention further provides a pharmaceutical composition comprising a compound described above and a pharmaceutically acceptable carrier. The pharmaceutically acceptable (e.g., pharmacologically acceptable) carriers include, for example, vehicles, adjuvants, excipients, or diluents, and 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 little or no detrimental side effects or toxicity under the conditions of use.

[0031] The choice of carrier will be determined in part by the particular active compound, 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 composition may be administered in any suitable formulation, for example, as a formulation for oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular, interperitoneal, intrathecal, rectal, or vaginal administration.

[0032] Formulations suitable for oral administration can comprise (a) liquid solutions, such as an effective amount of the compound 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 (compound), as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations can 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 corn starch. 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.

[0033] The compounds 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 can be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. 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 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.

[0034] 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 polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-β-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[0035] The parenteral formulations will typically contain from about 0.5 to about 25% by weight of the active ingredient 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. The quantity of surfactant in such formulations typically ranges from about 5 to about 15% by weight. Suitable surfactants include polyethylene or polyethylene glycol 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.

[0036] The compounds of the present invention 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).

[0037] Additionally, the compounds of the present invention 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.

[0038] The present invention further provides a method of preventing or treating a disease, or a condition that predisposes to a disease, that is characterized by or caused by the activation of the serine/threonine kinase Akt in an animal comprising administering to the animal a preventive or treatment effective amount of a compound described above. An example of a disease or condition is cancer. Particular examples of cancer include breast cancer, lung cancer, ovarian cancer, uterine cancer, brain cancer, sarcoma, melanoma, leukemia, lymphoma, colorectal cancer, prostate cancer, and liver cancer. Another disease or condition is rheumatologic disease, e.g., rheumatoid arthritis or osteoarthritis. A further example of the disease or condition is pulmonary disease, e.g., chronic obstructive pulmonary disease (COPD). The present invention further provides a method of increasing apoptosis of a cell, e.g., cancer cell, comprising contacting or treating the cell with a compound described above. The compounds of the present invention can be used as scientific tools to determine the presence of a disease or condition that are characterized by Akt activation.

[0039] They could be used alone or combined with other types of therapies to treat disease. Diseases characterized by Akt activation that could benefit from administration of the compounds include all forms of cancer, precancerous lesions, cardiovascular disease, rheumatologic disease, pulmonary disease, dermatologic disease, gynecological diseases, vascular disease, neurologic disease, and infectious disease, including bacterial, viral, retroviral, and parasitic diseases. Moreover, these compounds could be utilized to prevent above said diseases. Assays incorporating these compounds could provide predictive or prognostic value to patients with above said diseases or conditions.

[0040] Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the 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. Preferred dosages range from about 0.01 to about 10 mg/kg body weight/day, and further preferred dosages range from about 0.01 to about 1 mg/kg body weight/day.

[0041] The present invention further provides a method for inhibiting PH domain binding comprising exposing a material containing an PH domain to a compound described above. The present invention further provides a method for determining the presence of a PH domain in a material comprising:

(a) exposing a sample of the material to a PH domain binding compound and obtaining a first binding result;

(b) exposing another sample of the material to a compound of the present invention and obtaining a second binding result; and

(c) comparing the first and second binding results to determine whether a PH domain is present in the material.

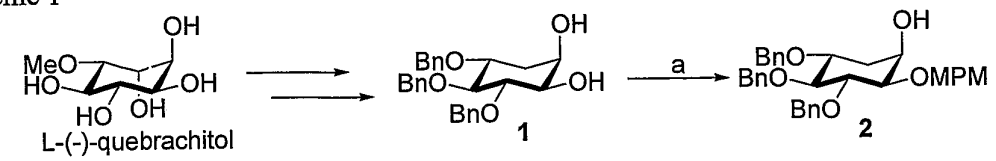
[0042] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0043] This Example illustrates a method of preparing precursors for 2-modified analogues.

[0044] This illustrates a method of preparing precursor for 3-deoxy 2-modified analogues. Compound **1** was prepared from L-(-)-quebrachitol according to a published method (*Tetrahedron*, *53*, 14903-14914 (1997)). Selective *p*-methoxybenzylation of the 1-OH in 1 via a 1,2-*O*-stannylene intermediate gave compound 2 (Scheme 1).

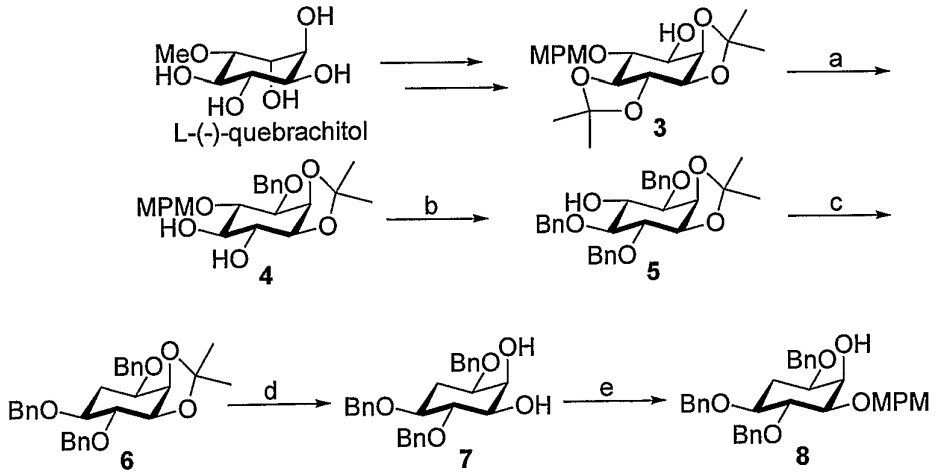
Scheme 1



Reagents and conditions: Bu_2SnO, toluene, reflux, then *p*-$MeOC_6H_4CH_2Cl$, CsF, DMF, rt, 92%.

[0045] This illustrates a method of preparing precursors for 4-deoxy 2-modified analogues. Compound **3** was prepared from L-quebrachitol (*Org. Lett. 2*, 115-117 (2000)). After benzyl protection of the 3-OH group, the trans-acetonide was selectively removed to give diol **4**. The two hydroxyl groups of 3 were protected by benzylation, and the MPM group at position 4 was removed by oxidation with ceric ammonium nitrate (CAN) to yield alcohol **5**. Barton-McCombie deoxygenation at C-4 gave compound **6**. Cleavage of the remaining acetonide in **6** gave diol **7**. Selective *p*-methoxybenzylation of the 1-OH of 7 in the same method as **2** gave compound **8** (Scheme 2).

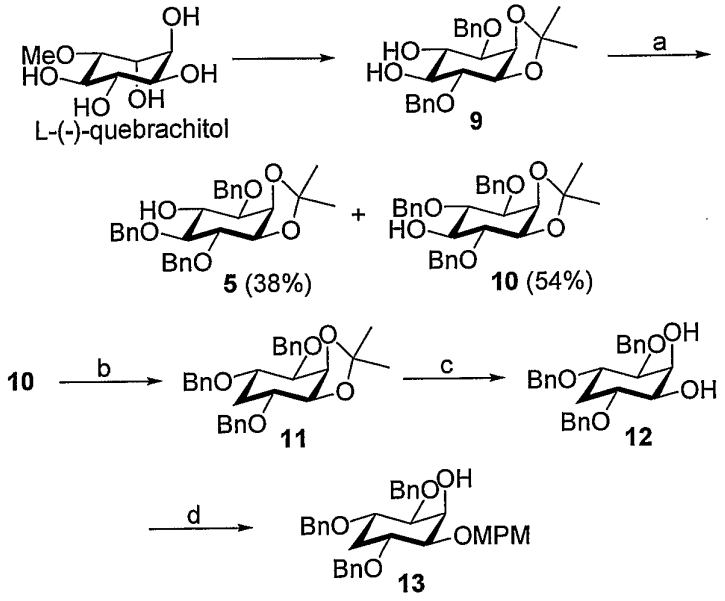
Scheme 2



Reagents and conditions: (a) (i) NaH, BnBr, DMF, 0 °C – rt; (ii) AcCl, CH_2Cl_2-MeOH 4:1 (v/v), rt, 86% for two steps; (b) (i) NaH, BnBr, 0 °C - rt, DMF; (ii) CAN, CH_3CN-H_2O 4:1 (v/v), 0 °C - rt, 84% for two steps; (c) (i) NaH, CS_2, 0 °C, DMF, then MeI; (ii) Bu_3SnH, AIBN, toluene, reflux, 95% for two steps; (d) AcCl, MeOH, rt, 98%; (e) Bu_2SnO, toluene, reflux, then *p*-$MeOC_6H_4CH_2Cl$, CsF, DMF, rt, 93%.

[0046] This illustrates a method of preparing a precursor for 5-deoxy-2-modified analogues. Compound **9** was synthesized according to a literature method (*Org. Lett.*, *2*, 115-117 (2000)). Mono-benzylation of the diol moiety of **9** via a 4,5-*O*-stannylene intermediate gave two compounds **5** and **10** in a ratio of 1:1.5, which were separated by careful chromatography on silica gel. Barton-McCombie deoxygenation at C-5 of compound **10** gave compound **11**. Cleavage of the trans-acetonide yielded diol **12**. Selective p-methoxybenzylation of the 1-OH of **12** in the same method as **2** gave compound **13** (Scheme 3).

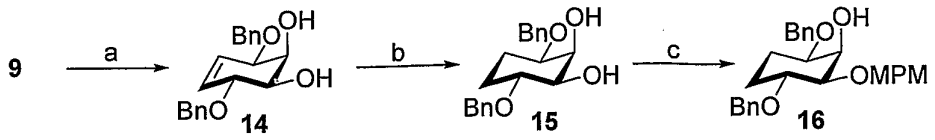
Scheme 3



Reagents and conditions: (a) Bu_2SnO, toluene, reflux, then BnBr, CsF, DMF, rt; (b) (i) NaH, CS_2, 0 °C, DMF, then MeI; (ii) Bu_3SnH, AIBN, toluene, reflux, 92% for two steps; (c) AcCl, MeOH, rt, 98%; (d) Bu_2SnO, toluene, reflux, then *p*-$MeOC_6H_4CH_2Cl$, CsF, DMF, rt, 92%.

[0047] This illustrates a method for preparing precursors for 4,5-dideoxy-2-modified analogues. Removal of the two hydroxyl groups in **9** by Barton-McCombie deoxygenation, followed by removal of the trans-acetonide gave olefinic diol **14**. Selective hydrogenation of the C = C double bond catalyzed by 5% Pd-C in ethyl acetate gave diol **15**. Selective *p*-methoxybenzylation of the 1-OH of **15** in the same method as **2** give compound **16** (Scheme 4).

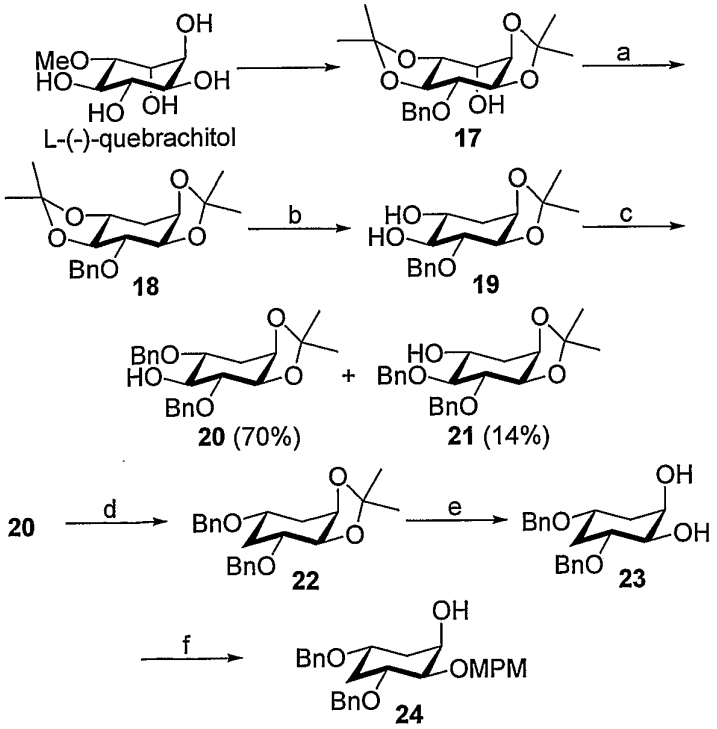
Scheme 4



Reagents and conditions: (a) (i) NaH, CS_2, 0 °C, DMF, then MeI; (ii) Bu_3SnH, AIBN, toluene, reflux; (iii) AcCl, MeOH, rt, 64% for three steps; (b) H_2, 5% Pd-C, ethyl acetate, rt, 1 atm, 95%; (c) Bu_2SnO, toluene, reflux, then *p*-$MeOC_6H_4CH_2Cl$, CsF, DMF, rt, 92%.

[0048] This illustrates a method for preparing precursors for 3,5-dideoxy-2-modified analogues. Compound **17** was synthesized according to a published procedure (*Org. Lett. 2*, 115-117 (2000)). Barton-McCombie deoxygenation at C-3 furnished compound **18**. Selective cleavage of the trans-acetonide gave diol **19**. Mono-benzylation of the diol moiety gave two compounds **20** and **21** in a ratio of 5:1. The structure of compound **21** was confirmed by transformation into a known intermediate in the synthesis of a 3,4-dideoxy PI analogue (*Tetrahedron Lett.*, *41*, 7415-7418 (2000)). Barton-McCombie deoxygenation at C-5 in intermediate **20** gave compound **22**. Cleavage of the second acetonide yielded diol **23**. Selective *p*-methoxybenzylation of the 1-OH of **23** in the same method as **2** give compound **24** (Scheme 5).

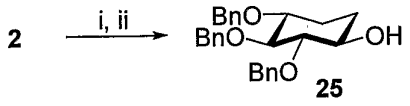
Scheme 5



Reagents and conditions: (a) (i) NaH, CS_2, 0 °C, DMF, then MeI; (ii) Bu_3SnH, AIBN, toluene, reflux, 94% for two steps; (b) AcCl, CH_2Cl_2-MeOH 4:1 (v/v), rt, 86%; (c) Bu_2SnO, toluene, reflux, then BnBr, CsF, DMF, rt; (d) (i) NaH, CS_2, 0 °C, DMF, then MeI; (ii) Bu_3SnH, AIBN, toluene, reflux, 93% for two steps; (e) AcCl, MeOH, rt, 96%; (f) Bu_2SnO, toluene, reflux, then *p*-$MeOC_6H_4CH_2Cl$, CsF, DMF, rt, 93%.

[0049] Barton-McCombie deoxygenation at C-2 in compound **2** followed by removal of the MPM group on 1-OH gave compound **25** (Scheme 6).

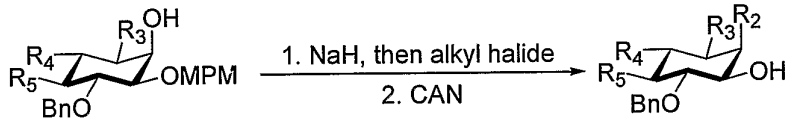
Scheme 6



Reagents and conditions: (i) NaH, CS_2, then MeI, 0 °C, DMF; (ii) Bu_3SnH, AIBN, toluene, reflux; (iii) CAN, CH_3CN-H_2O 4:1 (v/v), 0 °C – rt, 81% over two steps.

[0050] This illustrates a method of modifying position 2. The above precursors were alkylated with suitable alkyl halide to give a series of 2-modified compounds. The MPM group in these compounds was cleaved by oxidation with CAN to give a series of precursors for phosphorylation (Scheme 7).

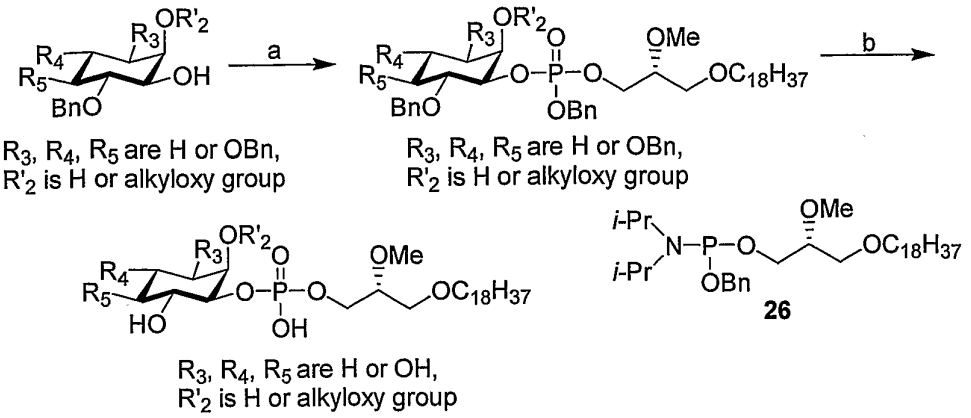
Scheme 7



R_3, R_4, R_5 are H or OBn, R_2 is H or alkyloxy group

[0051] The above precursors were phosphorylated by reaction with the ether lipid phosphoramidite **26** catalyzed by 1*H*-tetrazole and subsequent oxidation of the phosphite intermediates with *m*-CPBA to give a series of phosphates. Finally, these phosphates were completely deprotected by catalytic hydrogenation to give the desired analogues (Scheme 8).

Scheme 8



Reagents and conditions: (a) (i) **26**, 1*H*-tetrazole, rt, CH_2Cl_2; (ii) *m*-CPBA, 0 °C – rt, CH_2Cl_2; (b) H_2, 20% $Pd(OH)_2$-C, *t*-BuOH, rt, 1 atm.

EXAMPLE 2

[0052] This Example illustrates some of the properties of the compounds of the present invention. Figure 1D shows results of an immunoblotting experiment performed with antibodies against phosphorylated Akt at S473 and at native Akt after individual administration of the compounds to cancer cell lines. Phospho-specific antibodies only recognize kinases in an active state. Two cell lines were used that have high levels of constitutively active Akt, H1703 and H157. H1703 has wild type PTEN and H157 has mutant PTEN. Compounds SH5, 6, 13, 16, 23, 24, 25 decreased Akt phosphorylation without affecting native Akt levels.

[0053] All but SH16 also decreased Akt phosphorylation in the H157 cells. The lack of decreased phosphorylation observed with SH7 is important because SH7 is composed of only the ether lipid portion of these analogues and thus serves as a negative control. This data indicate that inhibition of Akt phosphorylation by some of the SH compounds is cell line specific, and that inhibition by SH5, 6, 13, 23-25 is not dependent on PTEN. Figure 1E shows that SH5, 6, 23-25 inhibit Akt kinase activity, as well as Akt phosphorylation.

[0054] Figure 1F shows results on some of the compounds. SH5, 6, 23, 24, and 25 completely inhibited Akt phosphorylation in all three cell lines and were chosen for further analysis.

[0055] Figure 2A is a set of representative immunoblotting experiments with increasing doses of SH5, 6, and 24. For each set of immunoblotting experiments, densitometry was performed to quantify the decreased intensity of the bands observed with the S473 antibodies. Quantitative inhibition of S473 phosphorylation by different doses of these

compounds is shown in Figure 2B. The IC50 values for these compounds (including SH23 and 25 (data not shown)) were similar, between 2-4 μM.

[0056] The SH compounds were tested against Akt and other kinases that are either upstream of Akt (PDK-1), downstream of Akt (c-Raf, 4EBP-1, p70S6K, FKHR, GSK-3, and/or AFX), or downstream of Ras (ERK, p38). Immunoblotting was carried out with phospho-specific antibodies to assess activation state of the kinases, and with native antibodies to assess changes in protein levels. Similar results were obtained with the H1703 (Figure 3A) or H157 cells (Figure 3B). SH5, 6, and 10 inhibited Akt phosphorylation without affecting native Akt levels. DPIEL and SH7 did not decrease Akt phosphorylation. Upstream of Akt, phosphorylation of PDK-1 was not affected by any SH compound. Of the downstream substrates, c-Raf phosphorylation and 4EBP-1 phosphorylation were decreased most. Decreased c-Raf phosphorylation correlated with increased ERK and p38 phosphorylation, which is consistent with the inhibitory effect of S259 phosphorylation by Akt on c-Raf activity. Of note, p38 phosphorylation was only decreased by DPIEL, indicating that the DPIEL used in these experiments was not inert.

[0057] SH 23-25 had similar effects in both H1703 (Figure 3C) and MB468 (Figure 3D) cells (H157 data not shown). In H1703 cells, phosphorylation of Akt, c-Raf, and 4-EBP-1 was decreased by SH23-25, but PDK-1 phosphorylation was unaffected. MB468 cells decreased Akt phosphorylation with administration of SH23-25 without decreasing PDK-1 phosphorylation. Some effects of SH23-25 were unique to the MB468 cells. Because MB468 cells had little endogenous phosphorylated c-Raf, we could not evaluate inhibition of c-Raf. Phosphorylation of 4EBP-1 was not affected by SH23-25, but phosphorylation of GSK-3 was decreased.

[0058] Cell lines containing high or low endogenous levels of Akt activity were treated with SH compounds and the cell apoptosis was measured. As shown in Figure 4, three cell lines with high levels of Akt activity, H1703, H157, and H1155 cells, increased apoptosis by 10-20 fold with administration of SH5 or 6. Increased apoptosis was also observed with administration of SH5 or 6 in MB468 cells (data not shown). SH7 had no effect on apoptosis, similar to DPIEL (data not shown). In contrast to cells with high levels of Akt, cells with low endogenous Akt levels (H1355 and A549 cells) did not undergo apoptosis in response to SH5, 6, or 7.

[0059] SH5, 6, 23, 24, and 25 are very active in decreasing Akt phosphorylation in a panel of cancer cell lines. These compounds decrease Akt phosphorylation as well as Akt kinase activity, with IC50s in the low micromolar range. These compounds appear to be specific for Akt, as the phosphorylation of the upstream kinase, PDK-1, is unaffected by any of the SH compounds, as is phosphorylation of ERK and p38, which are downstream of

Ras. Cell-line specific, selective inhibition of phosphorylation of substrates downstream of Akt, such as c-Raf, 4EBP-1, GSK-3, and/or FKHR/AFX was observed. These compounds selectively increased apoptosis in cancer cell lines that depend on Akt activity for survival. Phosphorylation of tuberin, 4EBP-1 and P70S6K (substrates that control protein translation) was inhibited by SH23, 24, and 25; and SH5-6 inhibited phosphorylation of tuberin and 4EBP-1. Phosphorylation of forkhead family members AFX and FKHR that control transcription was inhibited by SH23 or 25. Phosphorylation of GSK-3 and c-Raf was attenuated by SH23-25.

References

1. Datta et al., M. E. Cellular survival: a play in three Akts. *Genes Dev., 13,* 2905-2927 (1999).

2. Bellacosa et al., P. N. A retroviral oncogene, akt, encoding a serine-threonine kinase containing an SH2-like region. *Science, 25,* 274-277 (1991).

3. Coffer et al., Molecular cloning and characterisation of a novel putative protein-serine kinase related to the cAMP-dependent and protein kinase C families [published erratum appears in Eur J Biochem 1992 May 1;205(3):1217]. *Eur J Biochem., 201,* 475-481 (1991).

4. Jones et al., Molecular cloning and identification of a serine/threonine protein kinase of the second-messenger subfamily. *Proc Natl Acad Sci U S A, 88,* 4171-4175 (1991).

5. Balendran et al., PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus of PRK2. *Curr Biol., 9,* 393-404 (1999).

6. Delcommenne et al., Phosphoinositide-3-OH kinase-dependent regulation of glycogen synthase kinase 3 and protein kinase B/AKT by the integrin-linked kinase. *Proc Natl Acad Sci U S A, 95,* 11211-11216 (1998).

7. Lynch et al., Integrin-linked kinase regulates phosphorylation of serine 473 of protein kinase B by an indirect mechanism. *Oncogene, 18:* 8024-8032 (1999).

8. Toker et al., Akt/protein kinase B is regulated by autophosphorylation at the hypothetical PDK-2 site. *J Biol Chem., 275,* 8271-8274 (2000).

9. Filippa et al., Mechanism of protein kinase B activation by cyclic AMP-dependent protein kinase. *Mol Cell Biol., 19,* 4989-5000 (1999).

10. Yano et al., Calcium promotes cell survival through CaM-K kinase activation of the protein-kinase-B pathway. *Nature, 396,* 584-587 (1998).

11. Datta et al., Akt Phosphorylation of BAD Couples Survival Signals to the Cell-Intrinsic Death Machinery. *Cell, 91,* 231-241 (1997).

12. del Peso et al., Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt. *Science, 278,* 687-689 (1997).

13. Cardone et al., Regulation of cell death protease caspase-9 by phosphorylation [see comments]. *Science, 282,* 1318-1321 (1998).

14. Kang et al., Akt protein kinase enhances human telomerase activity through phosphorylation of telomerase reverse transcriptase subunit. *J Biol Chem., 274,* 13085-13090 (1999).

15. Brunet et al., Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell, 96,* 857-868 (1999).

16. Kops et al., Direct control of the Forkhead transcription factor AFX by protein kinase *B. Nature, 398,* 630-634 (1999).

17. Ozes et al., NF-kappaB activation by tumour necrosis factor requires the Akt serine-threonine kinase [see comments]. *Nature, 401,* 82-85 (1999).

18. Romashkova et al., NF-kappaB is a target of AKT in anti-apoptotic PDGF signalling [see comments]. *Nature, 401,* 86-90 (1999).

19. Dudek et al., Regulation of Neuronal Survival by the Serine-Threonine Protein Kinase Akt. *Science, 275,* 661-665 (1997).

20. Kauffmann-Zeh et al., Suppresion of c-Myc-induced apoptosis by Ras signalling through PI(3)K and PKB. *Nature, 385,* 544-548 (1997).

21. Kennedy et al., Akt/Protein kinase B inhibits cell death by preventing the release of cytochrome c from mitochondria. *Mol Cell Biol., 19,* 5800-5810 (1999).

22. Khwaja et al., Matrix adhesion and ras transformation both activate a phosphoinositide 3-OH kinase and protein kinase B/Akt cellular survival pathway. *The EMBO Journal, 16,* 2783-2793 (1997).

23. Kulik et al., Antiapoptotic Signalling by the Insulin-Like Growth Factor I Receptor, Phosphatidylinositol 3-Kinase, and Akt. *Molecular and Cellular Biology, 17,* 1595-1606 (1997).

24. Chen et al., Suppression of transforming growth factor-beta-induced apoptosis through a phosphatidylinositol 3-kinase/Akt-dependent pathway. *Oncogene, 17,* 1959-1968 (1998).

25. Crowder et al., Phosphatidylinositol 3-kinase and Akt protein kinase are necessary and sufficient for the survival of nerve growth factor-dependent sympathetic neurons. *J Neurosci, 18,* 2933-2943 (1998).

26. Eves et al., N. Akt, a target of phosphatidylinositol 3-kinase, inhibits apoptosis in a differentiating neuronal cell line. *Mol Cell Biol., 18,* 2143-2152 (1998).

27. Blair et al., Akt-dependent potentiation of L channels by insulin-like growth factor-1 is required for neuronal survival. *J Neurosci, 19,* 1940-1951 (1999).

28. Gerber et al., Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. Requirement for Flk-1/KDR activation. *J Biol Chem., 273,* 30336-30343 (1998).

29. Hausler et al., Protection of CD95-mediated apoptosis by activation of phosphatidylinositide 3-kinase and protein kinase B. Eur *J Immunol, 28,* 57-69 (1998).

30. Kulik et al. Akt-dependent and -independent survival signaling pathways utilized by insulin-like growth factor I. *Mol Cell Biol., 18,* 6711-6718 (1998).

31. Rohn et al., The opposing roles of the Akt and c-Myc signalling pathways in survival from CD95-mediated apoptosis. *Oncogene, 17,* 2811-2818 (1998).

32. Chalecka-Franaszek et al., Lithium activates the serine/threonine kinase Akt-1 and suppresses glutamate-induced inhibition of Akt-1 activity in neurons. *Proc Natl Acad Sci U S A, 96,* 8745-8750 (1999).

33. Rust et al., The bile acid taurochenodeoxycholate activates a phosphatidylinositol 3-kinase-dependent survival signaling cascade [In Process Citation]. *J Biol Chem., 275,* 20210-20216 (2000).

34. Testa., AKT plays a central role in tumorigenesis. *Proc Natl Acad Sci U S A, 98,* 10983-10985 (2001).

35. Brognard et al., Akt/protein kinase b is constitutively active in non-small cell lung cancer cells and promotes cellular survival and resistance to chemotherapy and radiation. *Cancer Res., 61,* 3986-3997 (2001).

36. Clark et al., Constitutive and inducible Akt activity promotes resistance to chemotherapy, trastuzumab, and tamoxifen in breast cancer cells. *Molec Canc Ther., 1,* 707-717 (2002).

[0060] 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.

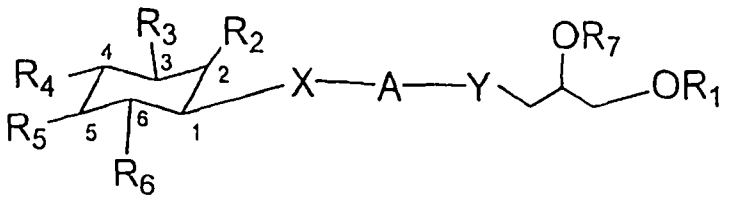
[0061] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. 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.

[0062] 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.

AUSTRALIAN PATENT APPLICATION NO. 2003270087
REVISED CLAIMS

1. A compound of the formula I:



(I)

or a pharmaceutically acceptable salt thereof;

wherein X and Y are independently selected from the group consisting of O, CF_2, CH_2, and CHF;

wherein A is independently selected from the group consisting of P(O)OH, CHCOOH, and $C(COOH)_2$;

R_2 is selected from the group consisting of H, OH, isosteres of OH, C_1-C_{25} alkyloxy, C_6-C_{10} aryloxy, C_3-C_8 cycloalkyloxy, C_3-C_8 cycloalkyl C_1-C_6 alkoxy, C_2-C_{22} alkenyloxy, C_3-C_8 cycloalkenyloxy, C_7-C_{32} aralkyloxy, C_7-C_{32} alkylaryloxy, C_9-C_{32} aralkenyloxy, and C_9-C_{32} alkenylaryloxy;

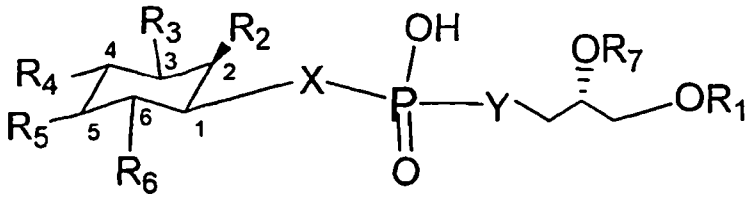
R_3-R_6 are independently selected from the group consisting of H, OH, and isosteres of OH selected from the group consisting of F, Cl, and SH; and

R_1 and R_7 are independently selected from the group consisting of C_1-C_{25} alkyl, C_6-C_{10} aryl, C_3-C_8 cycloalkyl, C_2-C_{22} alkenyl, C_3-C_8 cycloalkenyl, C_7-C_{32} aralkyl, C_7-C_{32} alkylaryl, C_9-C_{32} aralkenyl, and C_9-C_{32} alkenylaryl;

with the provisos that (i) when X is O, Y is O or CH_2, and R_3 is H, at least one of R_2 and R_4-R_6 is not OH; (ii) when A is CHCOOH or $C(COOH)_2$, X and Y cannot be simultaneously O; (iii) all of R_2-R_6 are not simultaneously H or OH; (iv) when X and Y are O, R_1 is $C_{18}H_{37}$, R_7 is methyl, and only one of R_2 and R_6 is alkoxy, then R_3 and R_5 are not simultaneously OH; and (v) when X and Y are O, R_1 is $C_{18}H_{37}$, R_3 is H, R_7 is methyl, and R_2, R_5, and R_6 are OH, then R_4 is not H or OH.

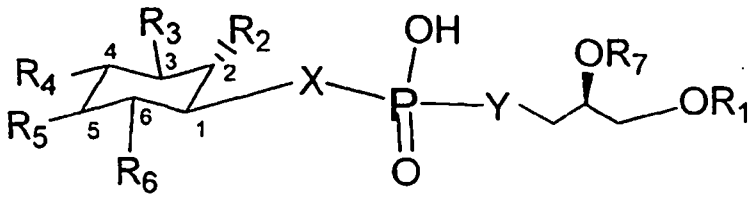
2. The compound or salt of claim 1, wherein A is P(O)OH.

3. The compound or salt of claim 1 or 2, wherein the compound has the formula Ia:



(Ia).

4. The compound or salt of claim 1 or 2, wherein the compound has the formula Ib:



(Ib).

5. The compound or salt of any of claims 2-4, wherein X and Y are O.

6. The compound or salt of any of claims 1-5, wherein R_1 is a C_1-C_{25} alkyl.

7. The compound or salt of any of claims 1-6, wherein R_7 is a C_1-C_{25} alkyl.

8. The compound or salt of any of claims 1-7, wherein R_2 is C_1-C_{25} alkyloxy, C_7-C_{32} aralkyloxy, or cyclohexylmethoxy.

9. The compound or salt of any of claims 1-7, wherein R_2 is H.

10. The compound or salt of any of claims 1-9, wherein R_3 is H.

11. The compound or salt of any of claims 1-10, wherein R_4 is H.

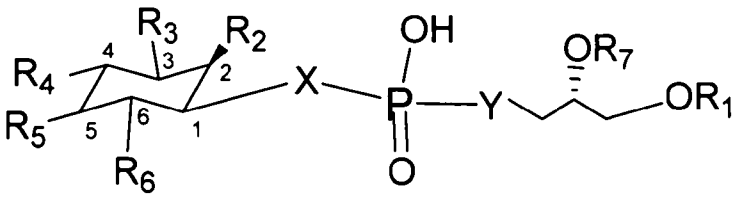
12. The compound or salt of any of claims 1-11, wherein R_5 is H.

13. The compound or salt of any of claims 1-12, wherein R_6 is H.

14. The compound or salt of claim 3, wherein X and Y are O, R_1 is $C_{18}H_{37}$, and R_7 is methyl.

15. The compound or salt of claim 14, wherein R_2-R_3 are H and R_4-R_6 are OH.

16. A compound of the formula:



wherein X and Y are O, R_1 is $C_{18}H_{37}$, R_7 is methyl, R_2-R_3 and R_5-R_6 are OH, and R_4 is H, or a pharmaceutically acceptable salt thereof.

17. The compound or salt of claim 14, wherein R_2 is i-butyloxy or cyclohexylmethoxy, R_3 is H, and R_4-R_6 are OH.

18. The compound or a pharmaceutically acceptable salt of claim 14, wherein R_2 is cyclohexylmethoxy, R_3 is H, and R_4-R_6 are OH.

19. The compound or pharmaceutically acceptable salt of claim 14, wherein R_2-R_4 and R_6 are OH and R_5 is H, or wherein R_2, R_4, and R_6 are OH and R_3 and R_5 are H.

20. A pharmaceutical composition comprising a compound or salt of any of claims 1-19 and a pharmaceutically acceptable carrier.

21. A method of preventing or treating a disease, or a condition that predisposes to a disease, which is characterized by the activation of the serine/threonine kinase Akt in an animal comprising administering to the animal a preventive or treatment effective amount of a compound or salt of any of claims 1-19.

22. The method of claim 21, wherein the disease is a cancer, a rheumatologic disease, a pulmonary disease, a precancerous lesion, a cardiovascular disease, a dermatologic disease, a gynecological disease, a vascular disease, a neurologic disease, or an infectious disease.

23. The method of claim 22, wherein the cancer is breast cancer, lung cancer, ovarian cancer, uterine cancer, brain cancer, sarcoma, melanoma, leukemia, lymphoma,

colorectal cancer, prostate cancer, or liver cancer.

24. The method of claim 22, wherein the rheumatologic disease is rheumatoid arthritis or osteoarthritis.

25. The method of claim 22, wherein the pulmonary disease is chronic obstructive pulmonary disease (COPD).

26. The method of claim 22, wherein the infectious disease is a bacterial, viral, retroviral, or parasitic disease.

27. A method of increasing apoptosis of a cell comprising contacting the cell with a compound or salt of any of claims 1-19.

28. A method for inhibiting PH domain binding comprising exposing a material containing an PH domain to a compound or salt of any of claims 1-19.

29. A method for determining the presence of a PH domain in a material comprising:

(a) exposing a sample of said material to a PH domain binding compound and obtaining a first binding result;

(b) exposing another sample of said material to a compound or salt of any of claims 1-19 and obtaining a second binding result; and

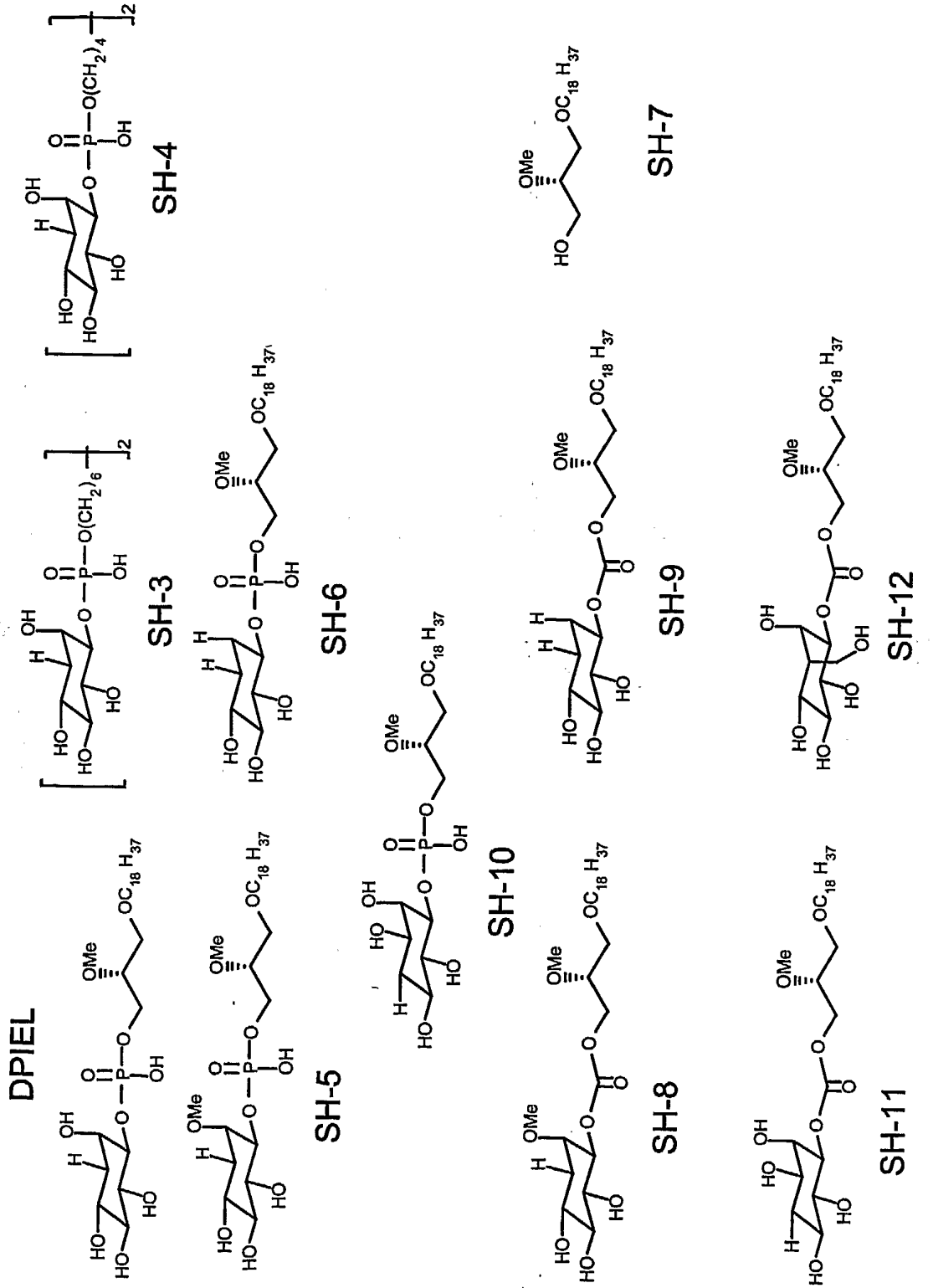
(c) comparing the first and second binding results to determine whether a PH domain is present in the material.

30. A compound or salt substantially as described herein with reference to the accompanying drawings and Examples.

31. A method of preventing or treating a disease or a condition that predisposes to a disease, substantially as described herein with reference to the accompanying drawings and Examples.

32. A method for determining the presence of a PH domain in a material, substantially as described herein with reference to the accompanying drawings and Examples.

FIG. 1A



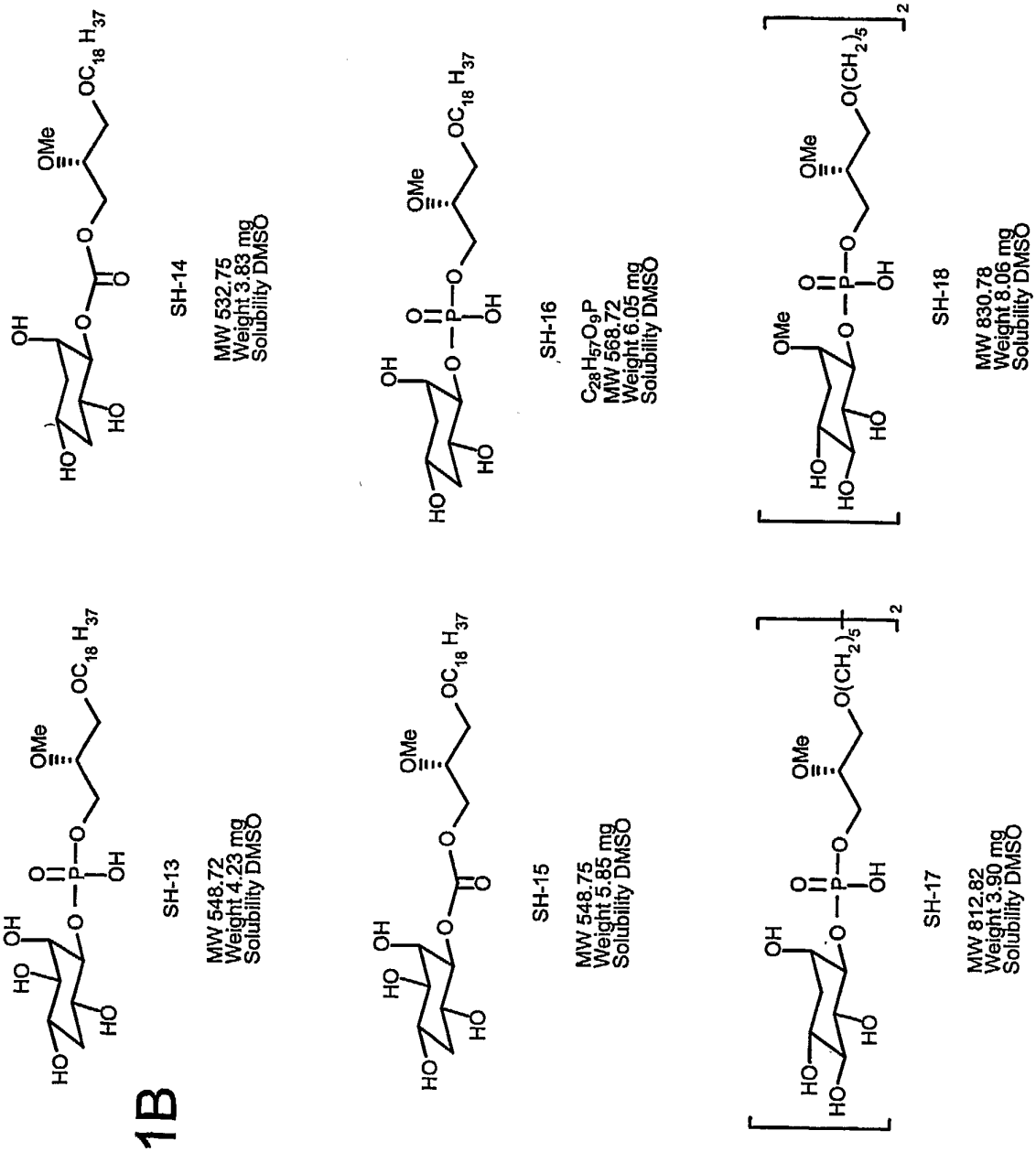
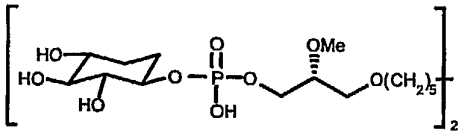

SH-13
MW 548.72
Weight 4.23 mg
Solubility DMSO
SH-14
MW 532.75
Weight 3.83 mg
Solubility DMSO
SH-15
MW 548.75
Weight 5.85 mg
Solubility DMSO
SH-16
$C_{28}H_{57}O_9P$
MW 568.72
Weight 6.05 mg
Solubility DMSO
SH-17
MW 812.82
Weight 3.90 mg
Solubility DMSO
SH-18
MW 830.78
Weight 8.06 mg
Solubility DMSO

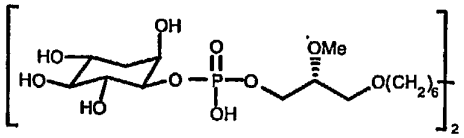
FIG. 1B

FIG. 1C



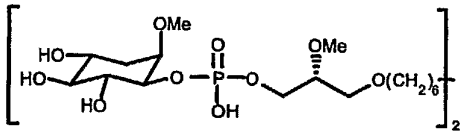
SH-19

MW 577.74
Weight 3.93 mg
Solubility DMSO



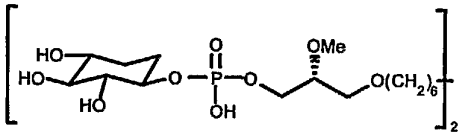
SH-20

MW 830.78
Weight 5.06 mg
Solubility DMSO



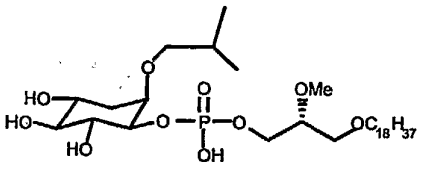
SH-21

MW 858.82
Weight 5.54 mg
Solubility DMSO

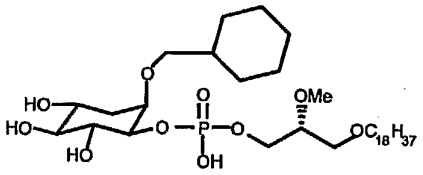


SH-22

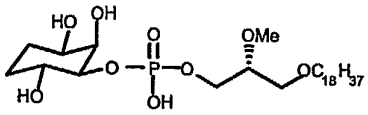
MW 798.78
Weight 5.90 mg
Solubility DMSO



SH-23
$C_{32}H_{65}O_{10}P$
MW 640.83
Weight 4.01 mg
Solubility DMSO



SH-24
$C_{36}H_{69}O_{10}P$
MW 680.89
Weight 4.85 mg
Solubility DMSO



SH-25
$C_{28}H_{57}O_9P$
MW 568.72
Weight 4.05 mg
Solubility DMSO

FIG. 1D

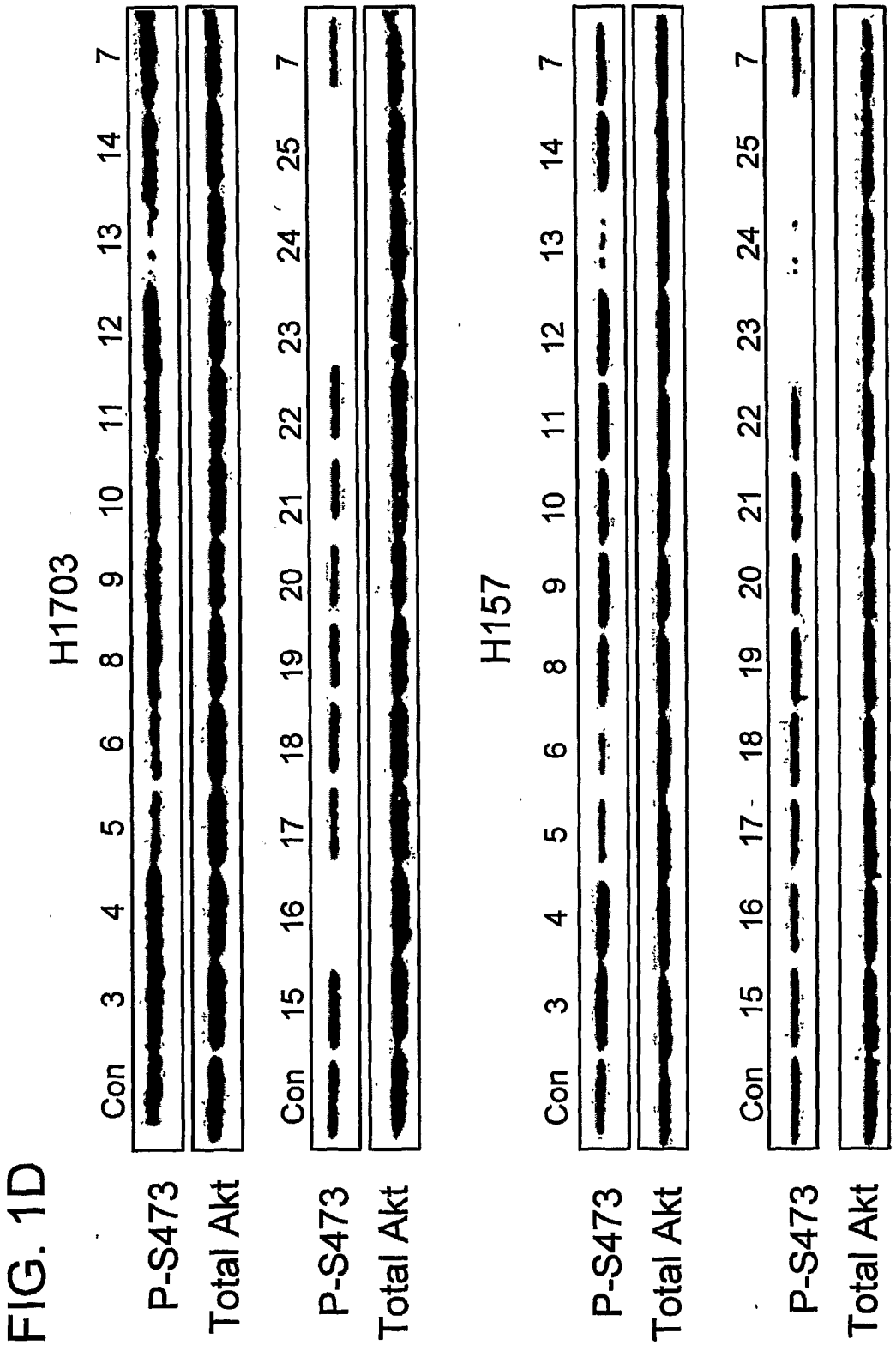

H1703
H157
Con 3 4 5 6 8 9 10 11 12 13 14 7
Con 15 16 17 18 19 20 21 22 23 24 25 7
P-S473
Total Akt

FIG. 1E

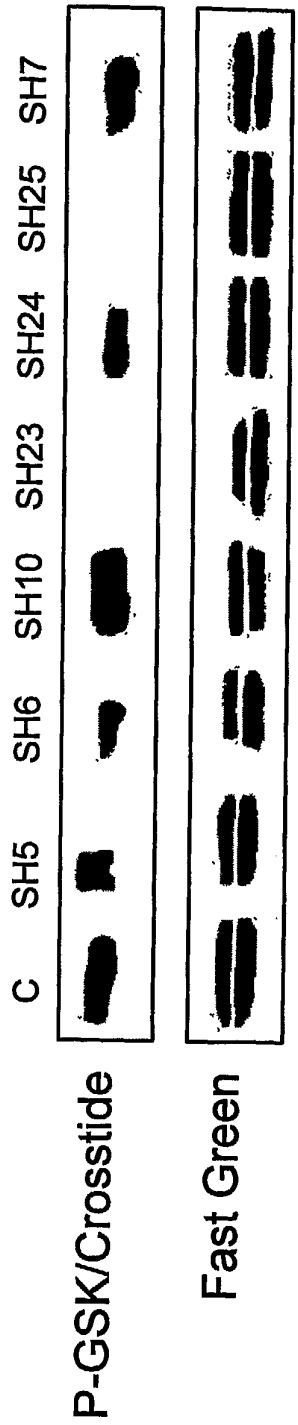
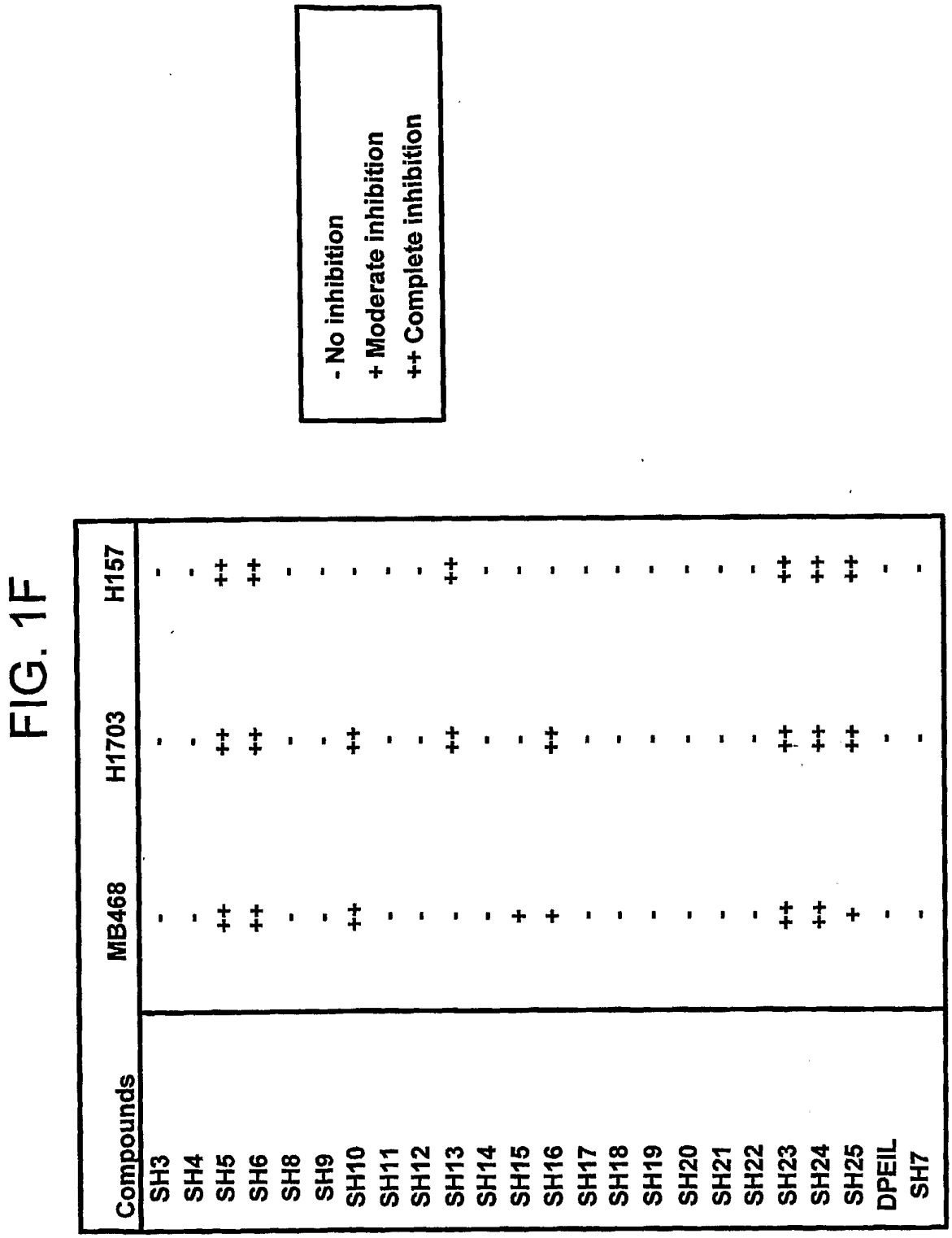


FIG. 1F



Compounds	MB468	H1703	H157
SH3	-	-	-
SH4	-	-	-
SH5	++	++	++
SH6	++	++	++
SH8	-	-	-
SH9	-	-	-
SH10	++	++	-
SH11	-	-	-
SH12	-	-	-
SH13	-	++	++
SH14	-	-	-
SH15	+	-	-
SH16	+	++	-
SH17	-	-	-
SH18	-	-	-
SH19	-	-	-
SH20	-	-	-
SH21	-	-	-
SH22	-	-	-
SH23	++	++	++
SH24	++	++	++
SH25	+	++	++
DPEIL	-	-	-
SH7	-	-	-

FIG. 2A

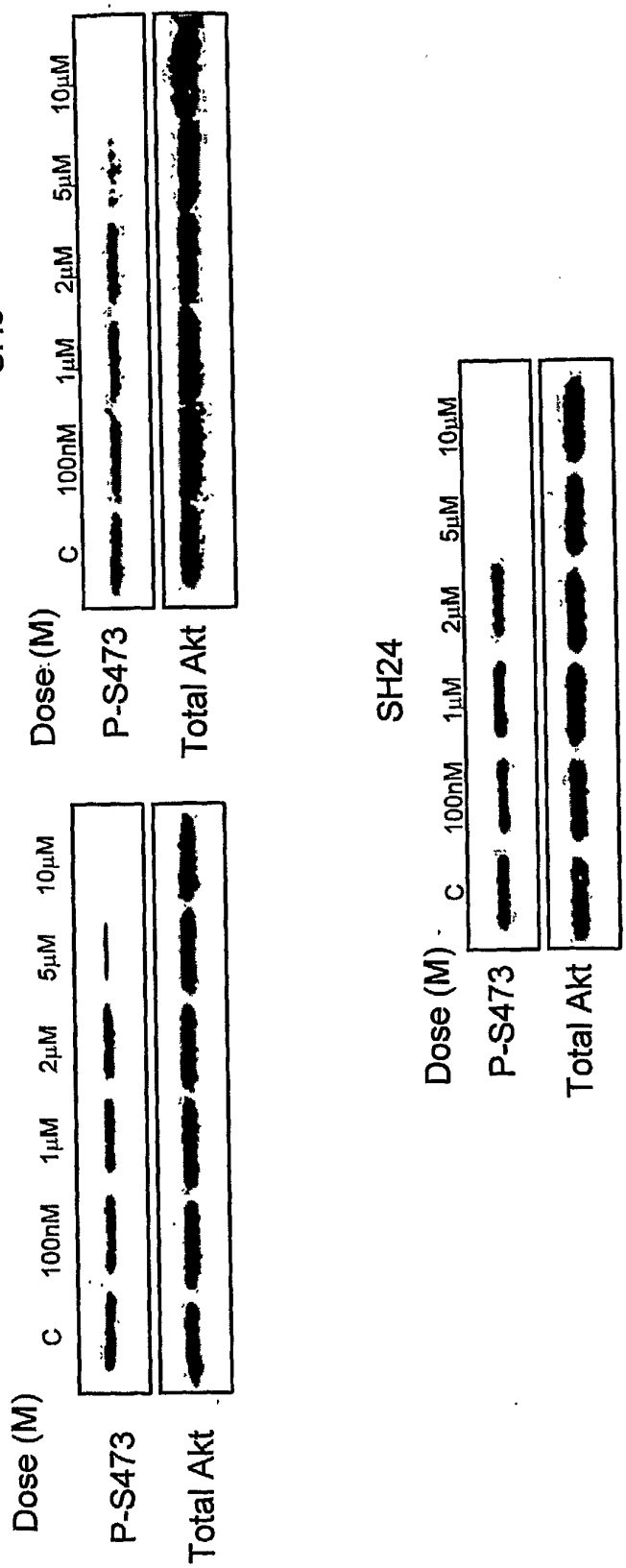

SH6
Dose (M)
C
100nM
1μM
2μM
5μM
10μM
P-S473
Total Akt
SH5
Dose (M)
C
100nM
1μM
2μM
5μM
10μM
P-S473
Total Akt
SH24
Dose (M)
C
100nM
1μM
2μM
5μM
10μM
P-S473
Total Akt

FIG. 2B

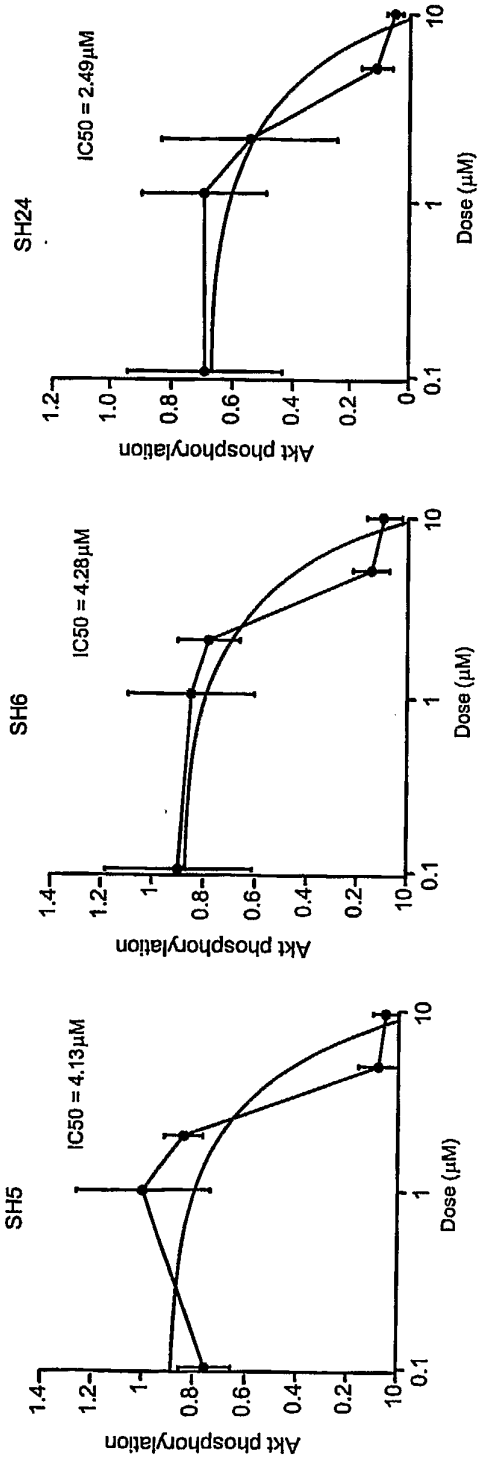

SH24
IC50 = 2.49μM
Akt phosphorylation
Dose (μM)
SH6
IC50 = 4.28μM
Akt phosphorylation
Dose (μM)
SH5
IC50 = 4.13μM
Akt phosphorylation
Dose (μM)

FIG. 3A

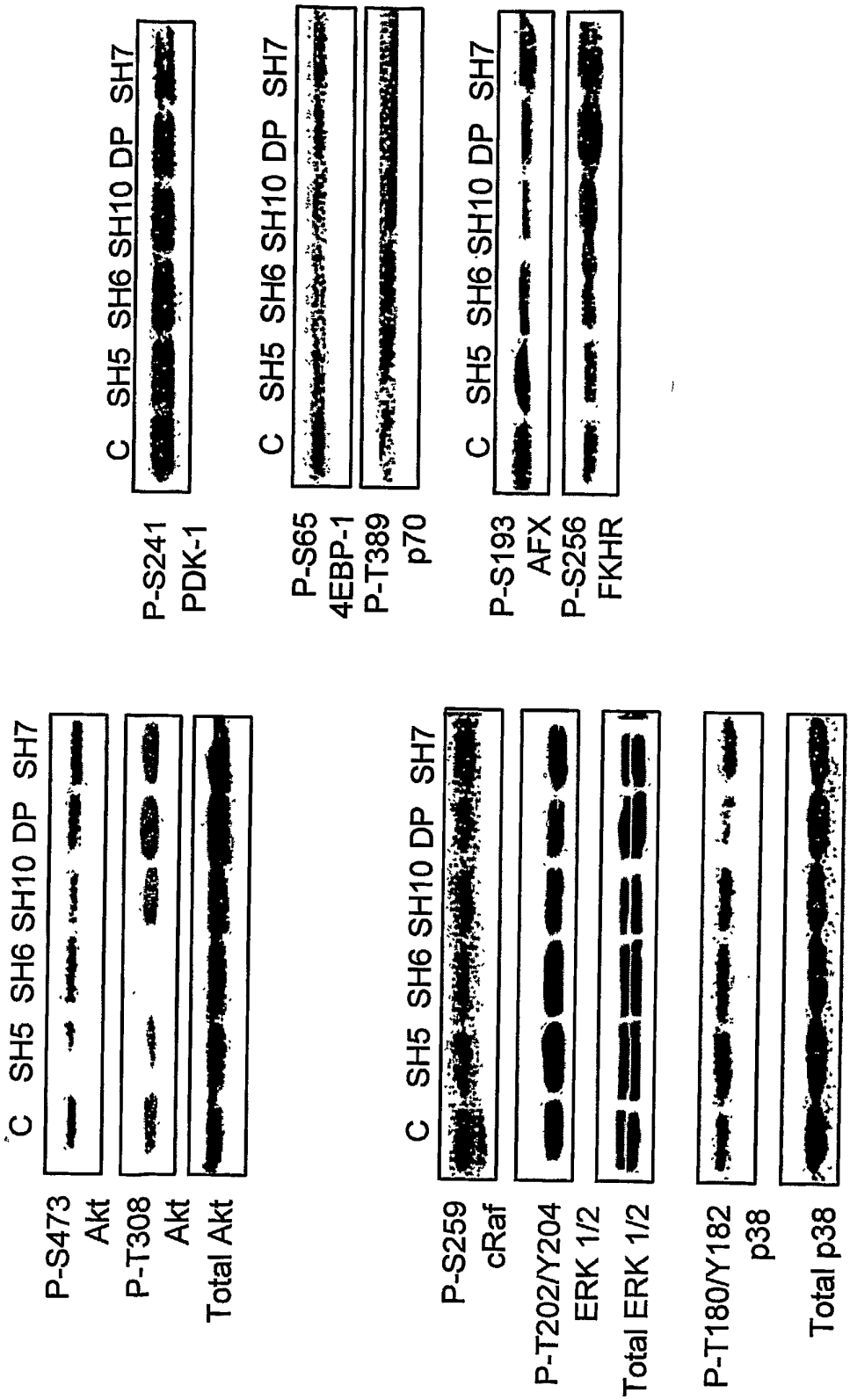

C SH5 SH6 SH10 DP SH7
P-S241 PDK-1
P-S65 4EBP-1
P-T389 p70
P-S193 AFX
P-S256 FKHR
P-S473 Akt
P-T308 Akt
Total Akt
P-S259 cRaf
P-T202/Y204 ERK 1/2
Total ERK 1/2
P-T180/Y182 p38
Total p38

FIG. 3B

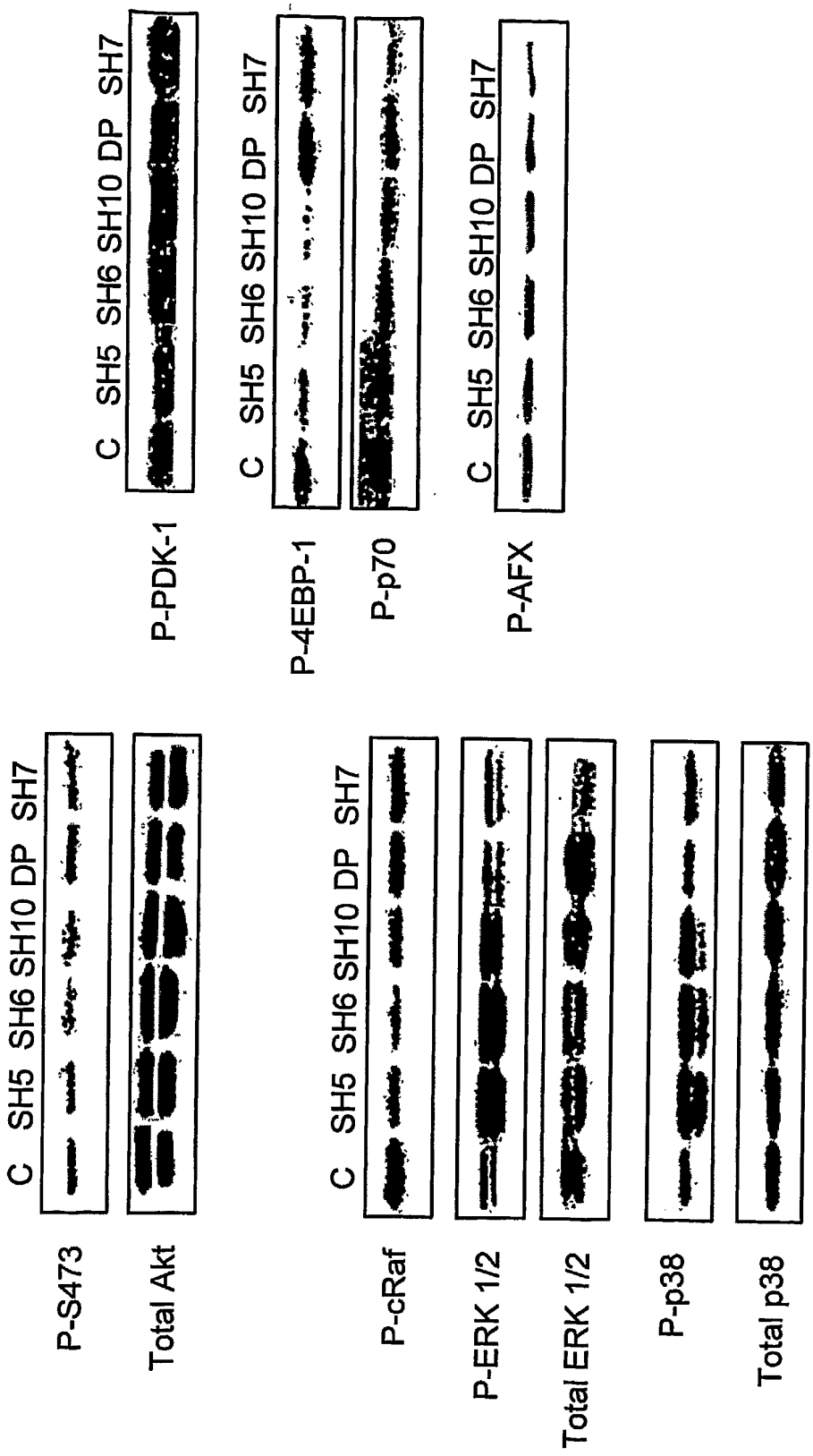

C SH5 SH6 SH10 DP SH7
P-S473
Total Akt
P-PDK-1
P-4EBP-1
P-p70
P-AFX
P-cRaf
P-ERK 1/2
Total ERK 1/2
P-p38
Total p38

FIG. 3C

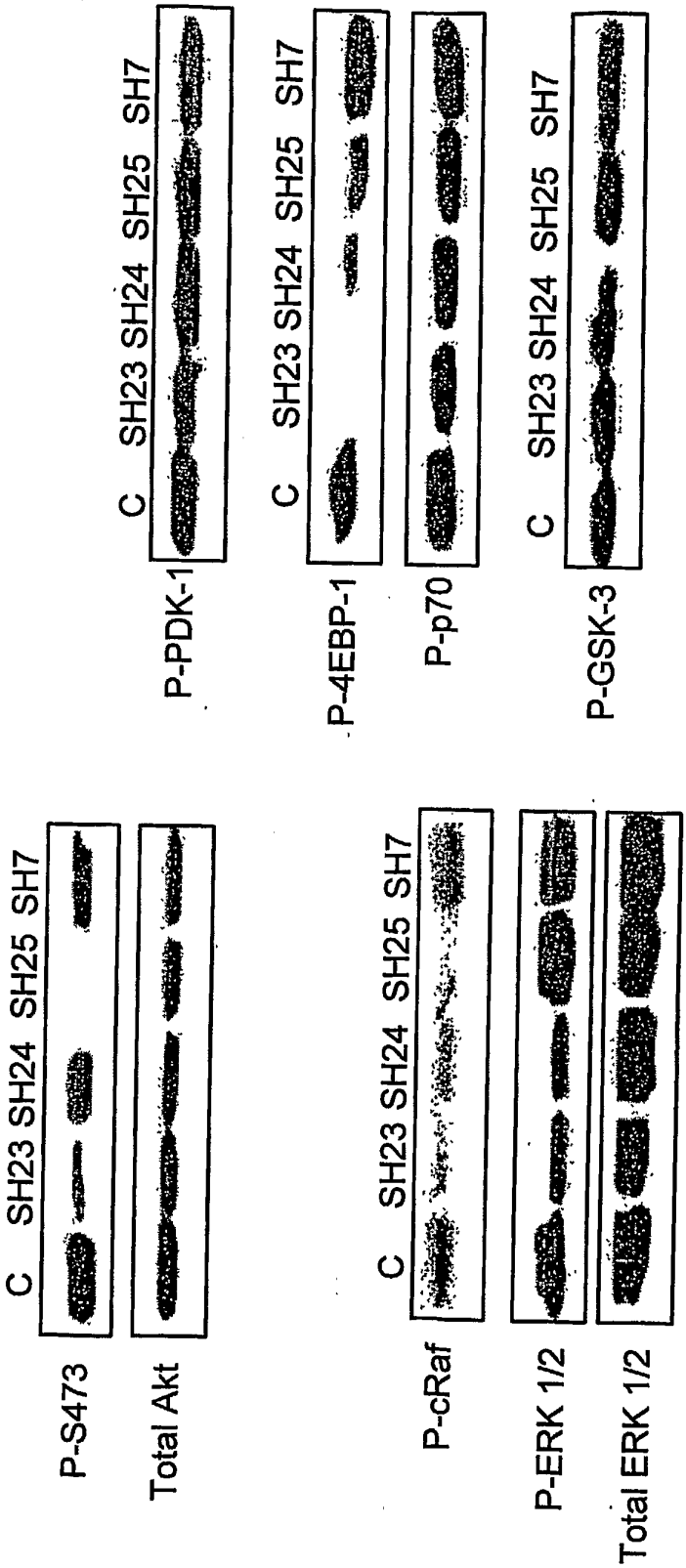

C SH23 SH24 SH25 SH7
P-PDK-1
P-4EBP-1
P-p70
P-GSK-3
P-S473
Total Akt
P-cRaf
P-ERK 1/2
Total ERK 1/2

FIG. 3D

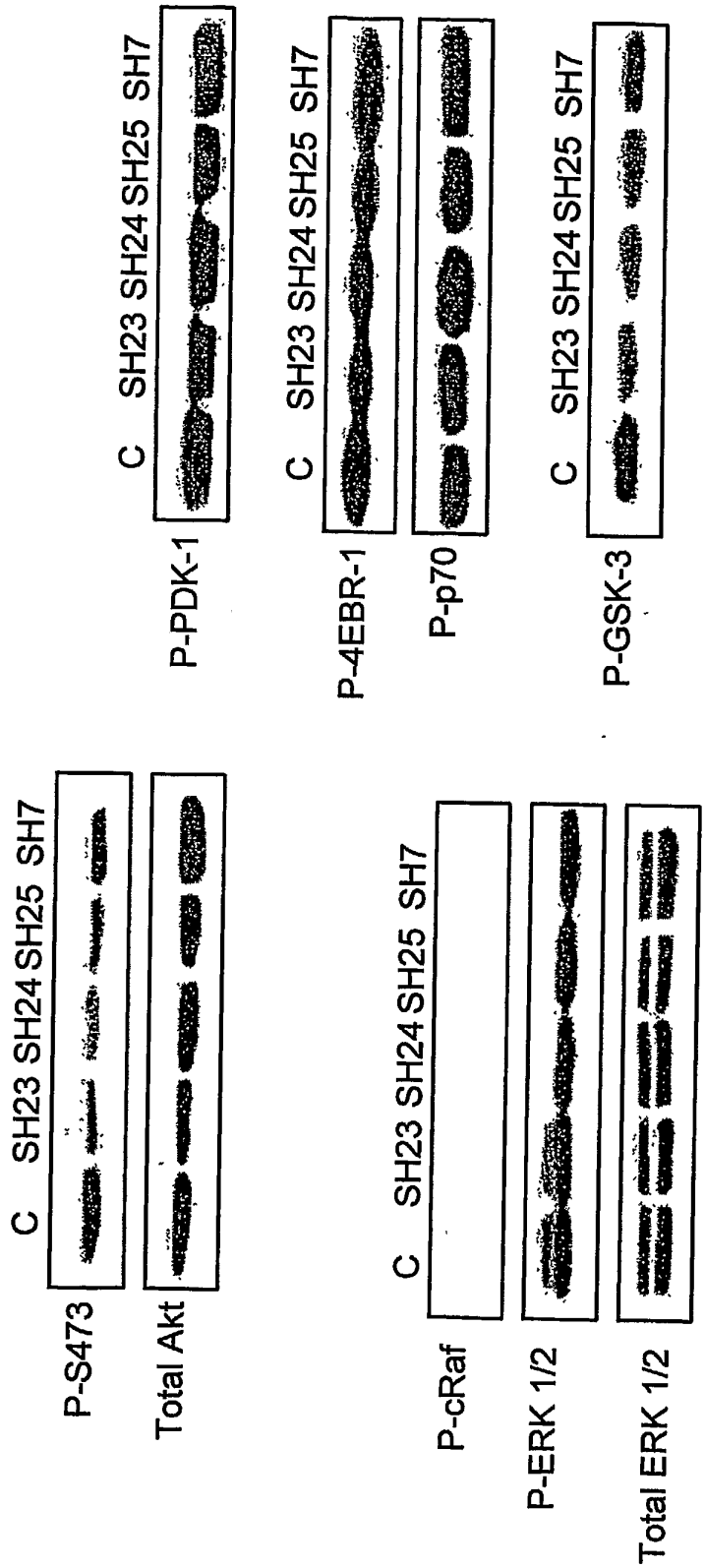
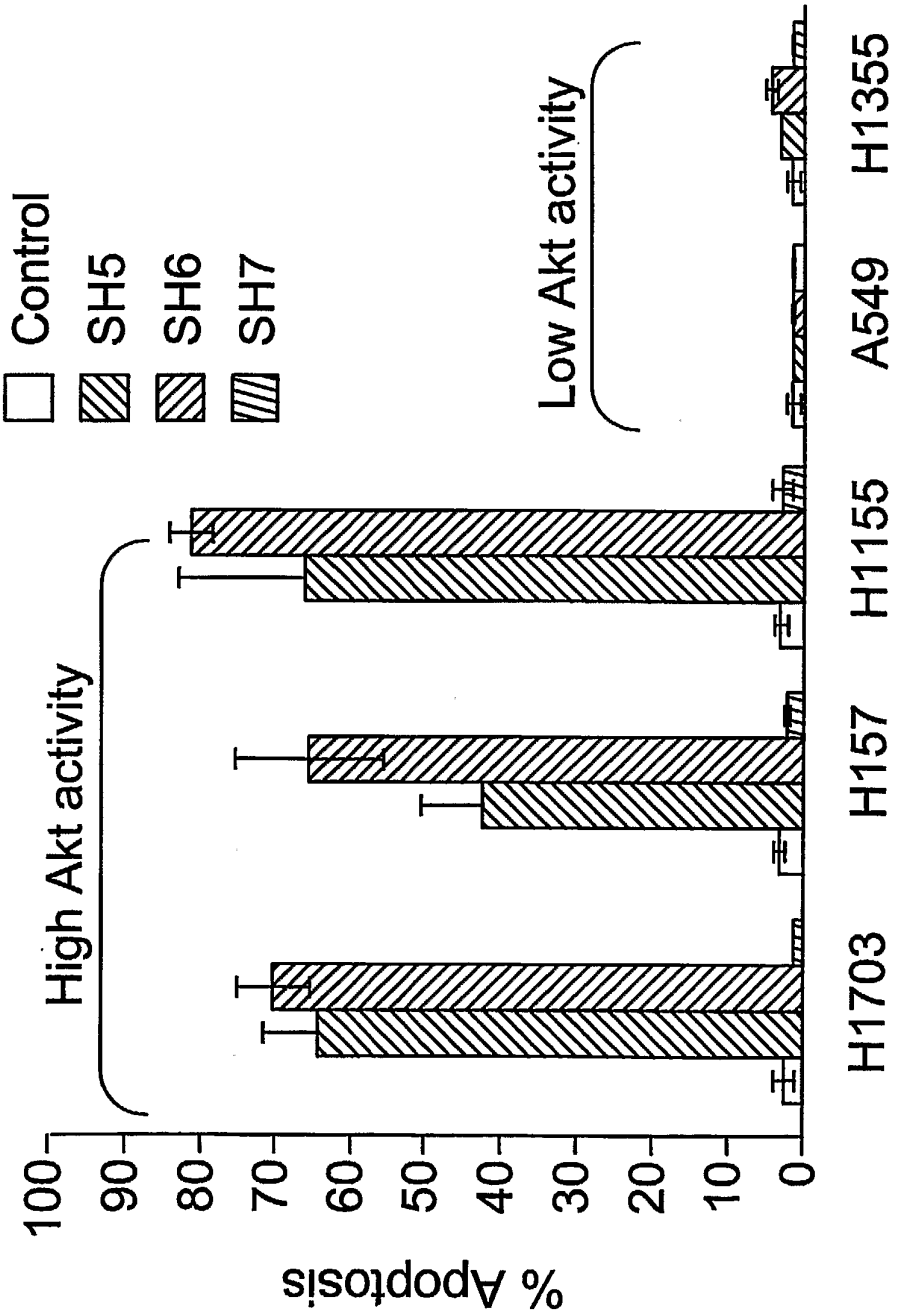

C SH23 SH24 SH25 SH7
P-S473
Total Akt
C SH23 SH24 SH25 SH7
P-PDK-1
C SH23 SH24 SH25 SH7
P-4EBR-1
P-p70
C SH23 SH24 SH25 SH7
P-GSK-3
C SH23 SH24 SH25 SH7
P-cRaf
P-ERK 1/2
Total ERK 1/2

FIG. 4


Control
SH5
SH6
SH7
High Akt activity
Low Akt activity
% Apoptosis
100
90
80
70
60
50
40
30
20
10
0
H1703
H157
H1155
A549
H1355