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(54) **Androgen receptor modulator for the treatment of prostate cancer and androgen receptor-associated diseases**

Androgenrezeptor-Modulator zur Behandlung von Prostatakrebs und androgenrezeptor-assoziierte Erkrankungen

Modulateurs de récepteurs d'androgènes pour le traitement du cancer de la prostate et de maladies liées au récepteur de l'androgène

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Description**FIELD OF THE INVENTION**

5 [0001] The present invention relates specific 8-oxo-6-thioxo-5,7-diazospiro[3,4]octan derivatives, their medical use in the treatment of androgens receptor-associated conditions, such as age-related diseases, for example, prostate cancer, and to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

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[0002] Prostate cancer is the most common incidence of cancer and the second leading cause of cancer death in Western men. When the cancer is confined locally, the disease can be cured by surgery or radiation. However, 30% of such cancer relapses with distant metastatic disease and others have advanced disease at diagnoses. Advanced disease is treated by castration and/or administration of anti-androgens, the so-called androgen deprivation therapy. Castration

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lowers the circulating levels of androgens and reduces the activity of androgen receptor (AR). Administration of anti-androgens blocks AR function by competing away androgen binding and therefore reduces the AR activity. Although initially effective, these treatments quickly fail and the cancer becomes hormone refractory.

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[0003] Recently, overexpression of AR has been identified and validated as a cause of hormone refractory prostate cancer (Nat. Med, 2004, 10, 33-39). Overexpression of AR is sufficient to cause progression from hormone sensitive to hormone refractory prostate cancer, suggesting that better AR inhibitors than the current drugs can slow the progression of prostate cancer. It was demonstrated that AR and its ligand binding are necessary for growth of hormone refractory prostate cancer, indicating that AR is still a target for this disease. It was also demonstrated that overexpression of AR converts anti-androgens from antagonists to agonists in hormone refractory prostate cancer (an AR antagonist inhibits AR activity and an AR agonist stimulates AR activity). Data from this work explain why castration and anti-androgens

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fail to prevent prostate cancer progression and reveals un-recognized properties of hormone refractory prostate cancer.

[0004] Bicalutamide (Brand name: Casodex) is the most commonly used anti-androgen. While it has inhibitory effect on AR in hormone sensitive prostate cancer, it fails to suppress AR when the cancer becomes hormone refractory. Two weaknesses of current antiandrogens are blamed for the failure to prevent prostate cancer progression from hormone sensitive stage to hormone refractory disease and to effectively treat hormone refractory prostate cancer. One is their weak antagonistic activities and the other is their strong agonistic activities when AR is overexpressed in hormone refractory prostate cancer. Therefore, better AR inhibitors with more potent antagonistic activities and minimal agonistic activities are needed to delay disease progression and to treat the fatal hormone refractory prostate cancer.

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[0005] Nonsteroidal anti-androgens, have been preferred over steroidal compounds for prostate cancer because they are more selective and have fewer side effects. A wide variety of such compounds were described in U.S. patent numbers 4,097,578, 5,411,981, and 5,705,654, U.S. published applications 2004/0009969 and 2007/0004753, and PCT international applications published as WO 97/00071, WO 00/17163 and WO 06/124118.

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[0006] Accordingly, identification of compounds which have high potency to antagonize the androgen activity, and which have minimal agonistic activity would overcome the hormone refractory prostate cancer (HRPC) and avoid or slowdown the progression of hormone sensitive prostate cancer (HSPC). There is a need in the art for the identification of selective modulators of the androgen receptor, such as modulators which are non-steroidal, non-toxic, and tissue selective.

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[0007] US 5646172 discloses spirocyclic imidazolidines having antiandrogenic activity. US 6172076 B1 discloses spirocyclic piperidines which inhibit prenyl-protein transferase and the prenylation of the oncogene protein Ras.

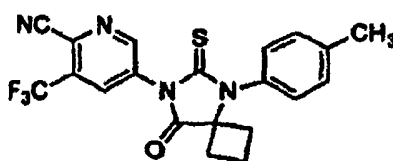
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SUMMARY OF THE INVENTION

[0008] A series of compounds that modulate the function of the nuclear hormone receptors, especially the androgen receptor are presented. These compounds can cause disappearance of prostate cancer cells and tumors.

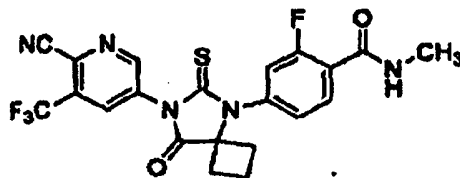
[0009] In an embodiment, the compound can be A51 or A52.

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A51



A52

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10 [0010] In an embodiment, a pharmaceutical composition includes a therapeutically effective amount of compound A51 or A52, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or adjuvant.

[0011] The Pharmaceutical composition can include a solution of dimethylsulfoxide, phosphate buffered saline solution, and water. The pharmaceutical composition can include dimethylsulfoxide, a carboxymethylcellulose, a polysorbate, and water.

15 [0012] An embodiment of a method includes preventing or treating a disease or disorder related to nuclear receptor activity.

[0013] A method for preventing or treating a hyperproliferative disorder, such as hormone sensitive prostate cancer or hormone refractory prostate cancer, can include administering compound A51 or A52, or a pharmaceutically acceptable salt thereof, to a subject in need of such prevention or treatment, thereby preventing or treating the hyperproliferative disorder. The compound can be administered at a dosage in the range of from about 1 mg per kg body weight per day to about 50 mg per kg body weight per day. The compound can be administered, for example, by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally.

20 [0014] In an embodiment, the compound A51 or A52 is an antagonist of a nuclear receptor or an antagonist of an androgen receptor.

25 DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 is a bar chart depicting the antagonist effect of compounds A51 and A52 on HS cancer cells.

[0016] Figure 2 is a bar chart depicting the antagonist effect of compounds A51 and A52 on HS cancer cells.

30 [0017] Figure 3 is a bar chart depicting the antagonist effect of compounds A51 and A52 on HR cancer cells.

[0018] Figure 4 is a graph depicting the pharmacokinetic behavior of compound A52.

[0019] Figure 5 is a graph depicting the effect of compound A52 on LnCaP-AR-overexpressed tumor size at 10 mg/kg.

[0020] Figure 6 presents images depicting the disappearance of Luciferase activity after 17 days of treatment with compound A52.

35 DETAILED DESCRIPTION

[0021] The present invention relates to the compounds A51 and A52, medical uses of such compounds as modulators of androgen receptors and to pharmaceutical compositions containing such compounds and salts thereof. Compounds A51 and A52 can be used to agonize or antagonize the function of the nuclear receptor. The compounds can be used to antagonize the androgen receptor. Use of the compounds is not limited to affecting the androgen receptor, but can, for example, also be useful for the treatment of other diseases related to nuclear receptor function.

40 [0022] The compounds A51 or A52 can be present as salts, which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred. If the compounds A51 or A52 have, for example, at least one basic center they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C1-C4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene-sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tert-butyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts can furthermore be formed. Salts

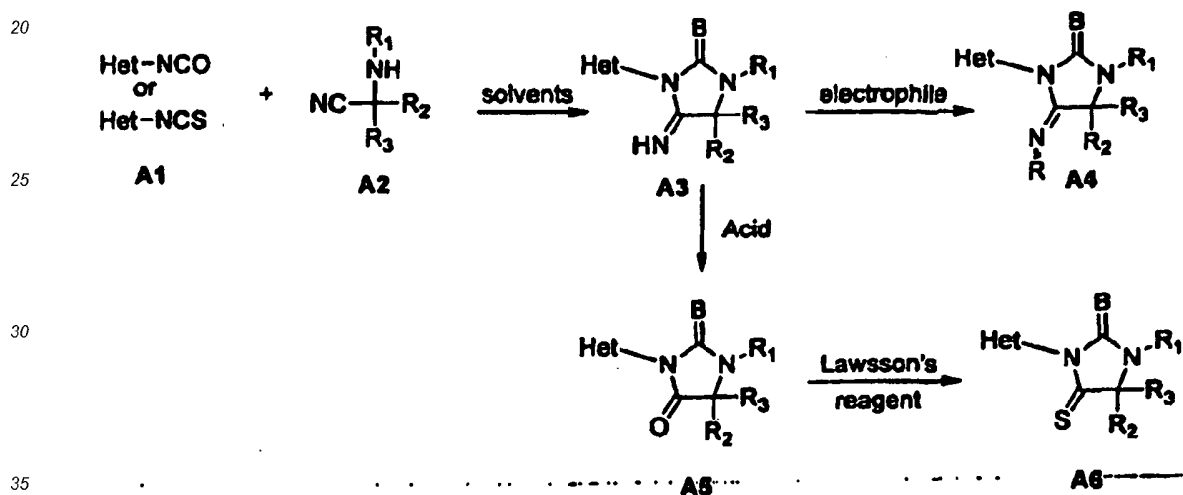
which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds or their pharmaceutically acceptable salts, are also included. Preferred salts of the compounds which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate. Preferred salts of the compounds which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

[0023] The term "modulator" used in this invention refers to a chemical compound with capacity to either enhance (e.g., "agonist" activity) or inhibit (e.g., "antagonist" activity) a functional property of biological activity or process (e.g., enzyme activity or receptor binding); such enhancement or inhibition can be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or can be manifest only in particular cell types.

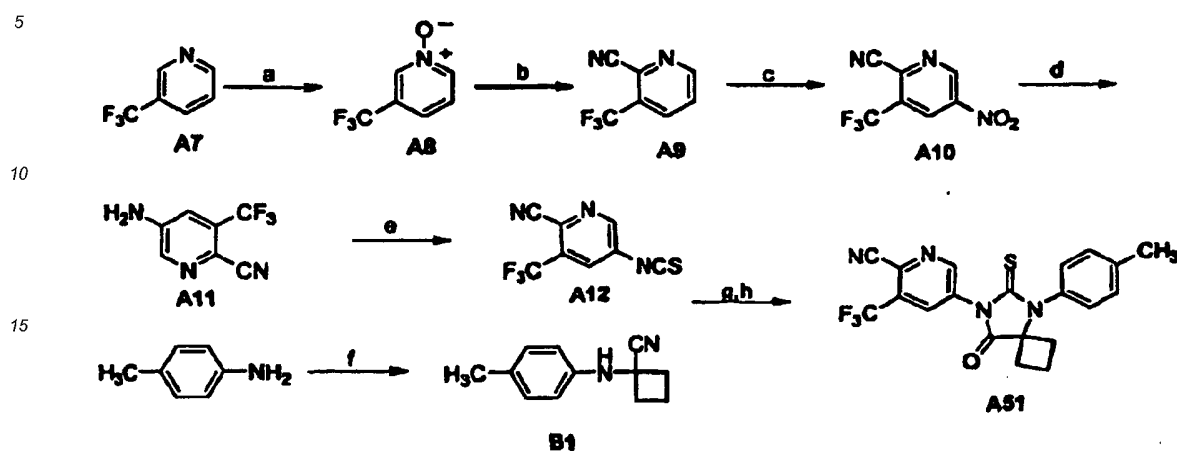
SYNTHESIS

[0024] The compounds A51 or A52 of the invention can be prepared as shown in the following reaction schemes and description thereof, as well as relevant published literature procedures that can be used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. The meaning of the variables is as in the compounds A51 or A52.

Scheme 1



[0025] As illustrated in Scheme 1, compounds of formula A4 can be prepared from intermediate A3 with an appropriate electrophile. Intermediates of formula A3 can be obtained by reacting intermediates A1 with A2 in an appropriate solvent such as N,N-dimethylformamide. Intermediates A1 and A2 can be obtained commercially, can be prepared by methods known in the literature, or can be readily prepared by one skilled in the art. Compounds of formula A3 can be treated with acid to afford compounds of formula A5. Compounds of formula A5 can be treated with Lawesson's reagent to obtain compounds of formula A6.

Scheme 2: Synthesis of A51Synthesis of 3-(trifluoromethyl)pyridine-N-oxide, A8

[0026] To a mixture of 3-(trifluoromethyl)pyridine **A7** (1.47 g, 10 mmol) and methyltrioxorhenium (0.0025g, 0.01 mmol) in dichloromethane (2 ml) was added 30% hydrogen peroxide (4 ml). The mixture was stirred at room temperature for 5 hours. A small portion of MnO₂ (3 mg) was added and the medium was stirred for an additional 1 hour and then dichloromethane was added (50 ml). The medium was washed with brine, dried over MgSO₄ and concentrated to obtain compound **A8** as an off-white powder (1.56 g, 9.6 mmol, 96%). ¹H NMR (400 MHz, CDCl₃) δ 7.22-7.23 (m, 2H), 8.15 (d, *J* = 3.6, 1H), 8.23 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 120.50 (q, *J* = 3.5 Hz), 121.58 (q, *J* = 271.4 Hz), 126.48, 130.10 (q, *J* = 34.5 Hz), 136.52 (q, *J* = 3.7 Hz), 141.89.

Synthesis of 2-cyano-3-(trifluoromethyl)pyridine, A9

[0027] To a solution of 3-(trifluoromethyl)pyridine-N-oxide **A8** (1.3 g, 8 mmol) in acetonitrile was added trimethylsilyl cyanide (0.99 g, 10 mmol) and triethylamine (2.02 g, 20 mmol). The mixture was stirred at room temperature for 24 hours and then was washed with saturated Na₂CO₃ and extracted with dichloromethane. The organic layer was dried over MgSO₄ and concentrated to yield a brown residue which was chromatographed (EtOAc: Pentane, 1:2). Compound **A9** was obtained as a light yellow solid (0.715g, 4.16 mmol, 52%). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, *J*₁ = 8.0 Hz, *J*₂ = 4.8 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.91 (d, *J* = 4.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 114.18, 121.74 (q, *J* = 272.3 Hz), 126.65, 130.45 (q, *J* = 33.8 Hz), 131.25, 134.66 (q, *J* = 4.2 Hz), 153.44.

Synthesis of 2-cyano-3-(trifluoromethyl)-5-nitropyridine, A10

[0028] To a mixture of **A9** (0.688 g, 4 mmol) and tetramethylammonium nitrate (1.09 g, 8 mmol) in 1,2-dichloroethane was added trifluoroacetic anhydride (1.68 g, 8 mmol). The mixture was sealed and heated to 60°C for 48 hours. The mixture was washed with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated to yield a yellow residue which was chromatographed (EtOAc: pentane, 1:4) to yield compound **A10** (0.095 g, 0.44 mmol, 11%) and the remaining starting material. ¹H NMR (400 MHz, CDCl₃) δ 8.91 (d, *J* = 2.4 Hz, 1H), 9.69 (d, *J* = 2.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 112.70, 120.65 (q, *J* = 273.5 Hz), 129.11, 130.40 (q, *J* = 4.4 Hz), 131.58 (q, *J* = 35.5 Hz), 144.22, 148.23.

Synthesis of 2-cyano-3-(trifluoromethyl)-5-aminopyridine, A11

[0029] A mixture of 2-cyano-3-(trifluoromethyl)-5-nitropyridine **A10** (0.095 g, 0.44 mmol) and iron powder (0.112 g, 2 mmol) in ethyl acetate (1 ml) and acetic acid (1 ml) was heated for 15 hours. The solid particle was filtered through Celite and the filtrate was concentrated and chromatographed (EtOAc: pentane, 1:1) to yield compound **A11** (0.075 g, 0.4 mmol, 91%). ¹H NMR (400 MHz, CDCl₃) δ 6.36 (bs, 2H), 7.38 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H).

[0030] Alternatively, 2-cyano-3-(trifluoromethyl)-5-nitropyridine **A10** can be reacted with hydrogen over Raney-Ni to obtain 2-cyano-3-(trifluoromethyl)-5-aminopyridine, **A11**.

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Synthesis of 5-isothiocyanato-3-trifluoromethylpyridine-2-carbonitrile, A12

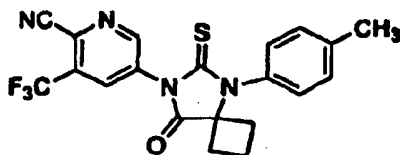
[0031] To a heterogeneous mixture of 2-cyano-3-(trifluoromethyl)-5-nitropyridine **A11** (0.075 g, 0.4 mmol) in water (2 ml) was added thiophosgene (50 μ l). The mixture was stirred for 2 hours and then washed with water and extracted with chloroform. The organic layer was dried over MgSO_4 and concentrated to yield compound **A12** (0.087g, 0.38 mmol, 95%). ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 2.4$ Hz, 1H), 8.72 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 113.61, 121.04 (q, $J = 273.1$ Hz), 127.41, 130.38 (q, $J = 4.3$ Hz), 131.44 (q, $J = 34.4$ Hz), 133.55, 144.75, 150.30.

Synthesis of 1-(4-methylphenyl)aminocyclobutanenitrile, B1

[0032] Trimethylsilyl cyanide (0.93 ml, 7 mmol) was added dropwise to a mixture of p-toluidine (0.535 g, 5 mmol) and cyclobutanone (0.42 g, 6 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **B1** (0.912 g, 4.9 mmol, 98%) as a yellowish solid.

Synthesis of 5-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-3-trifluoromethylpyridine-2-carbonitrile, A51

[0033] A mixture of **A12** (0.057g, 0.265 mmol) and **B1** (0.05 g, 0.265 mmol) in DMF (0.5 ml) was stirred at room temperature for 24 h. To this mixture were added methanol (2 ml) and aq. 2N HCl (1 ml). The second mixture was refluxed for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (20 ml). The organic layer was dried over MgSO_4 , concentrated and chromatographed (dichloromethane) to yield compound **A51** (0.066 g, 0.159 mmol, 60%) as a white powder.



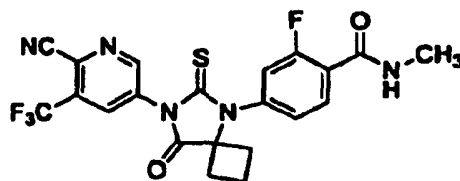
^1H NMR (CDCl_3 , 400 MHz) δ 1.63-1.73 (m, 1H), 2.17-2.28 (m, 1H), 2.47 (s, 3H), 2.55-2.71 (m, 4H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 8.39 (d, $J = 2.0$ Hz, 1H), 9.11 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 13.70, 21.38, 31.46, 67.61, 113.88, 121.36 (q, $J = 272.9$ Hz), 129.45, 129.73, 130.40 (q, $J = 34.3$ Hz), 130.86, 132.14, 132.53, 134.04 (q, $J = 4.3$ Hz), 140.33, 152.37, 174.74, 179.17.

N-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide, B2

[0034] Sodium cyanide (1.47 g, 30 mmol) was added to a mixture of N-methyl 4-amino-2-fluorobenzamide (1.68 g, 10 mmol) and cyclobutanone (1.4 g, 20 mmol) in 90% acetic acid (20 ml). The reaction mixture was stirred at 80 $^\circ\text{C}$ for 24 hours. The mixture was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to dryness under vacuum. The solid was washed with a 50:50 mixture of ethyl ether and hexane (10 ml) to remove cyclobutanone cyanohydrin to afford after filtration **B2** (2.19 g, 8.87 mmol, 89%). ^1H NMR (CDCl_3 , 400 MHz) δ 1.87-1.95 (m, 1H), 2.16-2.27 (m, 1H), 2.35-2.41 (m, 2H), 2.76-2.83 (m, 2H), 2.97 (d, $J = 4.4$ Hz, 3H), 4.68 (bs, 1H), 6.29 (dd, $J = 14.3, 1.8$ Hz, 1H), 6.48 (dd, $J = 8.3, 1.8$ Hz, 1H), 6.75 (q, $J = 4.4$ Hz, 1H), 7.90 (dd, $J = 8.3, 8.3$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 15.7, 26.7, 33.9, 49.4, 100.2 (d, $J = 29.5$ Hz), 110.6, 111.0 (d, $J = 11.8$ Hz), 133.1 (d, $J = 4.2$ Hz), 148.4 (d, $J = 12.0$ Hz), 162.0 (d, $J = 244.1$ Hz), 164.4 (d, $J = 3.6$ Hz).

Synthesis of 4-(7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl)-2-fluoro-N-methylbenzamide, A52

[0035] A mixture of **A12** (0.03 g, 0.13 mmol) and **B2** (0.032 g, 0.13 mmol) in DMF (0.5 ml) was heated under microwave irradiation at 80 $^\circ\text{C}$ for 20 hours. To this mixture was added methanol (2 ml) and aq. 2N HCl (1 ml). The second mixture was refluxed for 2 hours. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over MgSO_4 , concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield **A52** (0.022 g, 0.046 mmol, 35%) as a white powder.



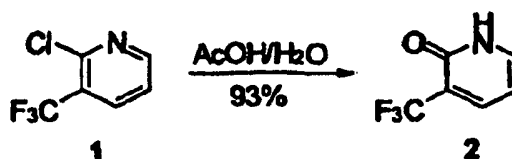
¹H NMR (CDCl₃, 400 MHz) δ 1.66-1.76 (m, 1H), 2.19-2.31 (m, 1H), 2.51-2.60 (m, 2H), 2.67-2.75 (m, 2H), 3.07 (d, *J* = 4.9 Hz, 3H), 6.75 (q, *J* = 4.8 Hz, 1H), 7.17 (dd, *J* = 11.4, 1.9 Hz, 1H), 7.26 (dd, *J* = 8.3, 1.9 Hz, 1H), 8.31 (dd, *J* = 8.3, 8.3 Hz, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 9.08 (d, *J* = 2.1 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 13.6, 27.0; 31.7, 67.6, 113.7, 118.1, 118.4, 121.4 (q, *J* = 272.9 Hz), 126.5, 130.0, 130.5 (q, *J* = 34.5 Hz), 132.2, 133.7, 134.0, (q, *J* = 4.2 Hz), 138.7 (d, *J* = 10.7 Hz), 152.2, 160.5 (d, *J* = 249.4 Hz), 162.6, 174.1, 179.0; ¹⁹F NMR (CDCl₃, 100 MHz) δ -110.94, -62.57.

Scheme 3: Synthesis of A52

[0036] In other embodiments, the present invention is directed to the method of synthesizing A52 described below. In some embodiments, Examples 1-8 can be performed sequentially to synthesize A52. However, as one of skill in the art will appreciate, this invention is not limited to the steps in Examples 1-8 as equivalent steps to those below are also encompassed by the present invention. Persons skilled in the art will recognize additional compounds that can be prepared utilizing similar methodology.

Synthesis of 3-(trifluoromethyl)pyridin-2(1H)-one, 2

[0037]

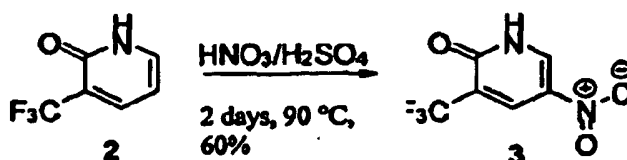


[0038] A solution of 2-chloro-3-(trifluoromethyl)pyridine **1** (5.00 g, 27.54 mmol) in a mixture of glacial acetic acid (50 ml) and water (5 ml) was refluxed for 7 days. The mixture was diluted with water (100 ml) and 6N aqueous NaOH was added until a pH of about 5 to about 6 was reached. The mixture was extracted with ethyl acetate (3 x 40 ml), the combined organic phases were dried over Na₂SO₄, and then all solvents were removed under reduced pressure. The resulting residue was dissolved in ethyl acetate and hexane was added to precipitate a product. After filtration, 3-(trifluoromethyl)pyridin-2(1H)-one **2** was obtained as an off-white powder (4.16 g, 25.51 mmol, 93%).

¹H NMR (400 MHz, DMSO) δ 12.31 (bs, 1H), 7.91 (d, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 6.4 Hz, 1H), 6.30 (t, *J* = 6.7 Hz, 1H).¹

Synthesis of 5-nitro-3-(trifluoromethyl)pyridin-2(1H)-one, 3

[0039]



[0040] A mixture of 3-(trifluoromethyl)pyridin-2(1H)-one **2** (2.00 g, 12.26 mmol) and sulfuric acid (H₂SO₄, 3.5 ml, 30%) was heated to 90 °C and nitric acid (HNO₃, 2.5 ml, 65%) was added. The mixture was stirred at 90 °C for 8 hours and additional nitric acid (1 ml, 65%) was added. The mixture was stirred for an additional 6 hours at 90 °C and was then poured into a beaker containing ice (30 ml). The mixture was diluted with water (30 ml) and 6N aqueous NaOH was added until a pH of about 4 to about 5. The mixture was extracted with ethyl acetate (3 x 40 ml), the combined organic phases dried over Na₂SO₄ and all solvents were removed under reduced pressure. The residue was dissolved in ethyl

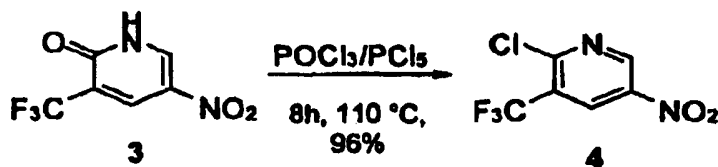
acetate and the product precipitated by the addition of hexane. After filtration, 5-nitro-3-(trifluoromethyl)pyridin-2(1H)-one **3** was obtained as a yellow powder (1.58 g, 7.59 mmol, 62%).

¹H NMR (400 MHz, DMSO) δ 13.47 (bs, 1H), 8.95 (d, $J = 2.7$ Hz, 1H), 8.46 (d, $J = 2.5$ Hz, 1H).²

5 Synthesis of 2-chloro-5-nitro-3-(trifluoromethyl)pyridine, 4

[0041]

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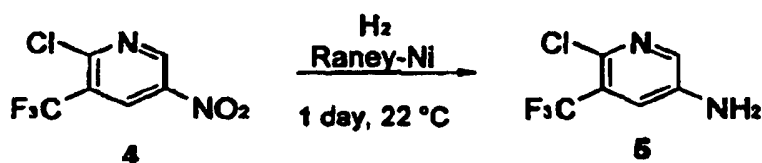
[0042] A mixture of 5-nitro-3-(trifluoromethyl)pyridin-2(1H)-one **3** (1.50 g, 7.21 mmol), POCl₃ (2.76 g, 18.02 mmol) and PCl₅ (1.4g, 10.09 mmol) is heated to about 110-120°C for 8 hours and then poured into ice water. The mixture is neutralized with solid NaHCO₃ and extracted with ethyl acetate (3 x 40 ml). The combined organic phases is dried over Na₂SO₄ and all solvents removed under reduced pressure to obtain 2-chloro-5-nitro-3-(trifluoromethyl)pyridine **4**.

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Synthesis of 6-chloro-5-(trifluoromethyl)pyridin-3-amine, 5

[0043]

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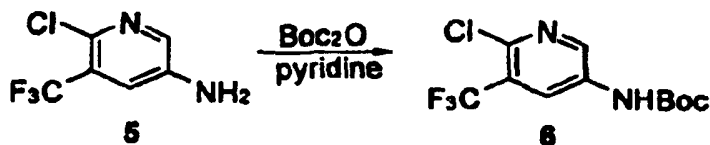
[0044] 2-Chloro-5-nitro-3-(trifluoromethyl)pyridine **4** (1.57 g, 6.93 mmol) is dissolved in tetrahydrofuran (THF) (10ml) and added to a suspension of Raney-Ni (200 mg) in THF (20 ml). Hydrogen gas is slowly bubbled through the stirred solution for 24 hours using a balloon. The mixture is filtered through Celite® (available from Word Minerals, Inc., Lompoc, California) and the solvent is removed under reduced pressure to obtain 6-chloro-5-(trifluoromethyl)pyridin-3-amine **5**.

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Synthesis of 1,1-dimethylethylcarbamate N-6-chloro-5-(trifluoromethyl)pyridin-3-yl, 6

[0045]

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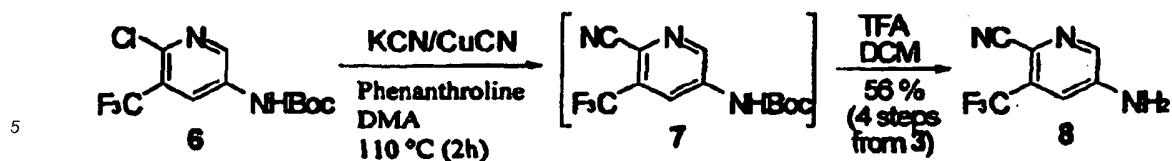
[0046] The crude 6-chloro-5-(trifluoromethyl)pyridin-3-amine **5** (1.3 g crude, 6.61 mmol) is dissolved in pyridine (10 ml) and 4-dimethylaminopyridine (DMAP) (50 mg) is added. Di-*tert*-butyl dicarbonate (2.17 g) is added dropwise and mixture stirred at 22 °C for 4 hours. Toluene (20 ml) is added and all solvents is removed under reduced pressure. The residue is filtered through a plug of silica gel (hexane/ethyl acetate 2:1) to obtain *tert*-butyl N-6-chloro-5-(trifluoromethyl)pyridin-3-ylcarbamate **6**.

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Synthesis of 5-amino-3-(trifluoromethyl)pyridine-2-carbonitrile, 8

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[0047]

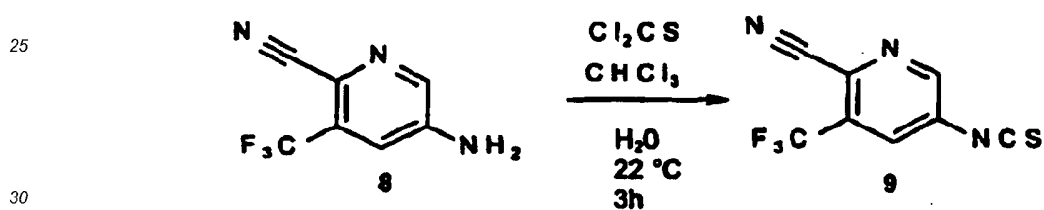


10 [0048] The crude *tert*-butyl *N*-6-chloro-5-(trifluoromethyl)pyridin-3-ylcarbamate **6** (2.4 g, 6.61 mmol) is dissolved in dimethylacetamide (DMA) (25 ml) and phenanthroline (120 mg, 0.66 mmol) is added. The mixture is heated to 80 °C and KCN (0.47 g, 7.27 mmol) is added. After stirring the mixture stirred for 10 min, CuCN (118 mg, 0.13 mmol) is added and the mixture stirred for 2 hours at 110 °C. The cooled mixture is poured into a phosphate buffer (150 ml, pH 7), ethyl acetate (50 ml) is added and the mixture is filtered through Celite®. The layers are separated and the aqueous phase is extracted with ethyl acetate (3 x 40 ml). The combined organic phases are washed With saturated aqueous NaCl (4 x 30 ml), dried over Na₂SO₄ and all solvents removed under reduced pressure to produce the crude *N*-*t*-butoxycarbonyl nitrile **7**.

15 [0049] The crude *N*-*t*-butoxycarbonyl nitrile **7** is dissolved in dichloromethane (20 ml) and trifluoroacetic acid (TFA) (4 ml) is added. The mixture is stirred for 3 hours and evaporated. The residue is purified by column chromatography on silica gel (hexane/ethyl acetate 2:1) to obtain 5-amino-3-(trifluoromethyl)pyridine-2-carbonitrile **8**.

20 Synthesis of 5-isothiocyanato-3-(trifluoromethyl)pyridine-2-carbonitrile, **9**

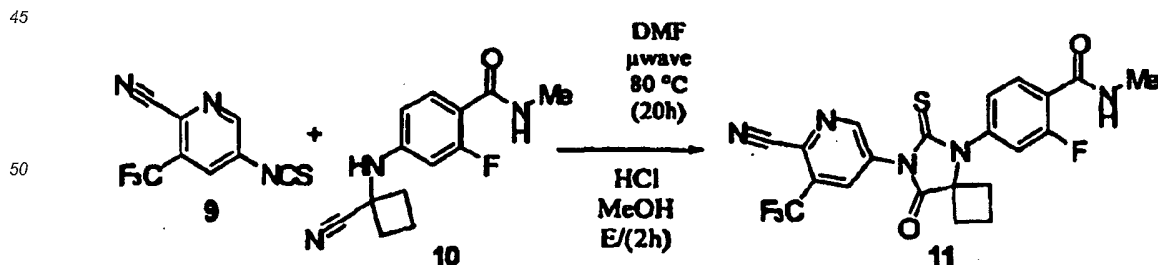
[0050]



35 [0051] 5-Amino-3-(trifluoromethyl)pyridine-2-carbonitrile **8** (1.141 g, 6.1 mmol) is mixed with chloroform (5 ml) and water (40 ml) to give a white suspension. Thiophosgene (0.701 ml, 9.15 mmol) is added and the reaction stirred for 2 hours at 22 °C to give a clear biphasic system. Chloroform (20 ml) is added and the phases are separated. The aqueous layer is extracted with chloroform (30 ml) and the combined organic is washed with saturated aqueous NaHCO₃ and water, dried over MgSO₄ and the solvent is removed under reduced pressure. The crude 5-isothiocyanato-3-(trifluoromethyl) pyridine-2-carbonitrile **9** is dried under vacuum and used as such in the next step, for example, in the step described in Example 8 below.

40 Synthesis of 4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluoro-*N*-methylbenzamide **11**. **A52**

[0052]



55 [0053] Crude 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile **9** (1.390 g, 6.07 mmol) is placed in a 50 mL round-bottomed flask and 4-(1-cyanocyclobutylamino)-2-fluoro-*N*-methylbenzamide **10** (0.5 g, 2.022 mmol) is added to the flask. The mixture is left under vacuum (using an oil pump) for 1 hour. *N,N*-dimethylformamide (DMF) (6 ml) is added, the flask sealed under argon with a stopper and heated to 80 °C in a CEM microwave reactor for 20 hours. Methanol

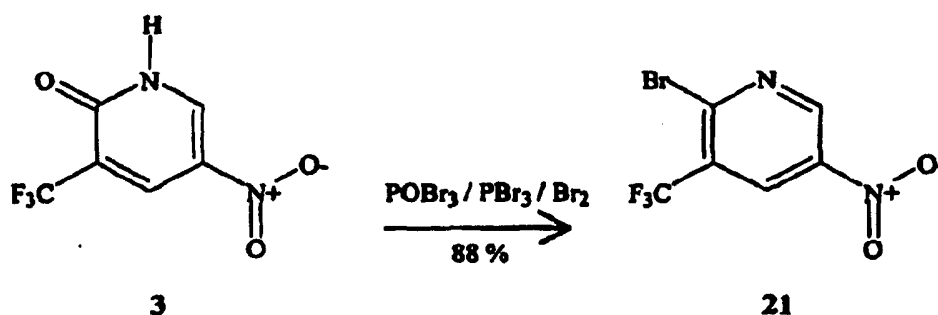
(10 ml) and 2N HCl (6 ml) is added and the mixture is refluxed for 2 hours. The mixture is diluted with water (30 ml) and saturated aqueous NaHCO₃ (30 ml) is added. The mixture is extracted with ethyl acetate (3 x 20 ml).

[0054] The combined organic layers is washed with saturated aqueous NaCl (20 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product is purified by column chromatography on silica gel (dichloromethane/acetone 95:5) to obtain 4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluoro-N-methylbenzamide **11**.

Scheme 4: Synthesis of A52

Example 1: Synthesis of 2-bromo-5-nitro-3-(trifluoromethyl)pyridine, 21

[0055]



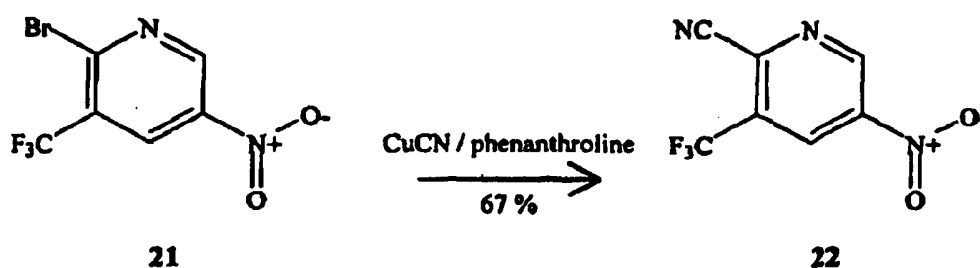
[0056] 5-nitro-3-(trifluoromethyl)pyridin-2(1H)-one **3** is obtained by the routes provided in Examples 1 and 2 of Scheme 3, above.

[0057] A mixture of 5-nitro-3-(trifluoromethyl)pyridin-2(1H)-one **3**, POBr₃ (1.5 equivalents), PBr₃ (4 equivalents), and Br₂ (2 equivalents) is heated to about 90-110 °C and is then poured into ice water. The mixture is neutralized and extracted. The combined organic phases are dried over Na₂SO₄ and all solvents removed under reduced pressure to obtain 2-bromo-5-nitro-3-(trifluoromethyl)pyridine **21** in a yield of 88%.

[0058] Alternatively, POBr₃ is substituted by POCl₃ to yield a mixture in the product having a ratio of bromine to chlorine substituents of 6:1 or better.

Synthesis of 5-nitro-3-(trifluoromethyl)pyridine-2-carbonitrile, 22

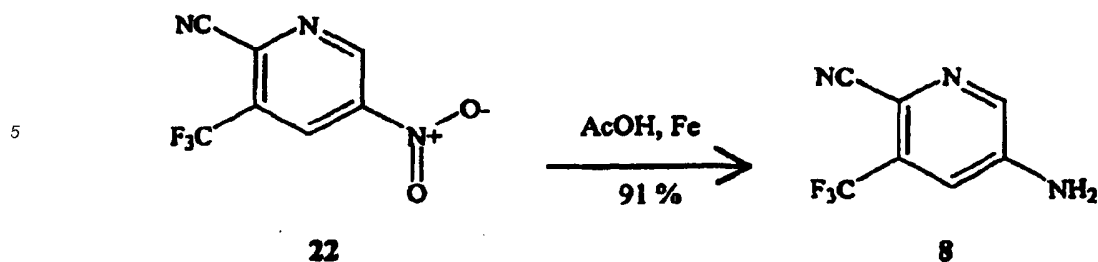
[0059]



[0060] The crude 2-bromo-5-nitro-3-(trifluoromethyl)pyridine **21** is dissolved in dimethylacetamide (DMA) and phenanthroline (0.2 equivalents) is added. The mixture is heated to 160 °C and CuCN (2 equivalents) is added. The mixture is stirred for 40 minutes. Chromatography is performed to produce the 5-nitro-3-(trifluoromethyl)pyridine-2-carbonitrile **22** in a yield of 67%.

Synthesis of 5-amino-3-(trifluoromethyl)pyridine-2-carbonitrile, 8

[0061]



10 [0062] A mixture of 5-nitro-3-(trifluoromethyl)pyridine-2-carbonitrile **22** and iron powder in acetic acid is heated. 5-amino-3-(trifluoromethyl)pyridine-2-carbonitrile, **8** is obtained in a yield of 91 %.

15 Synthesis of 4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluoro-N-methylbenzamide **11**, **A52**

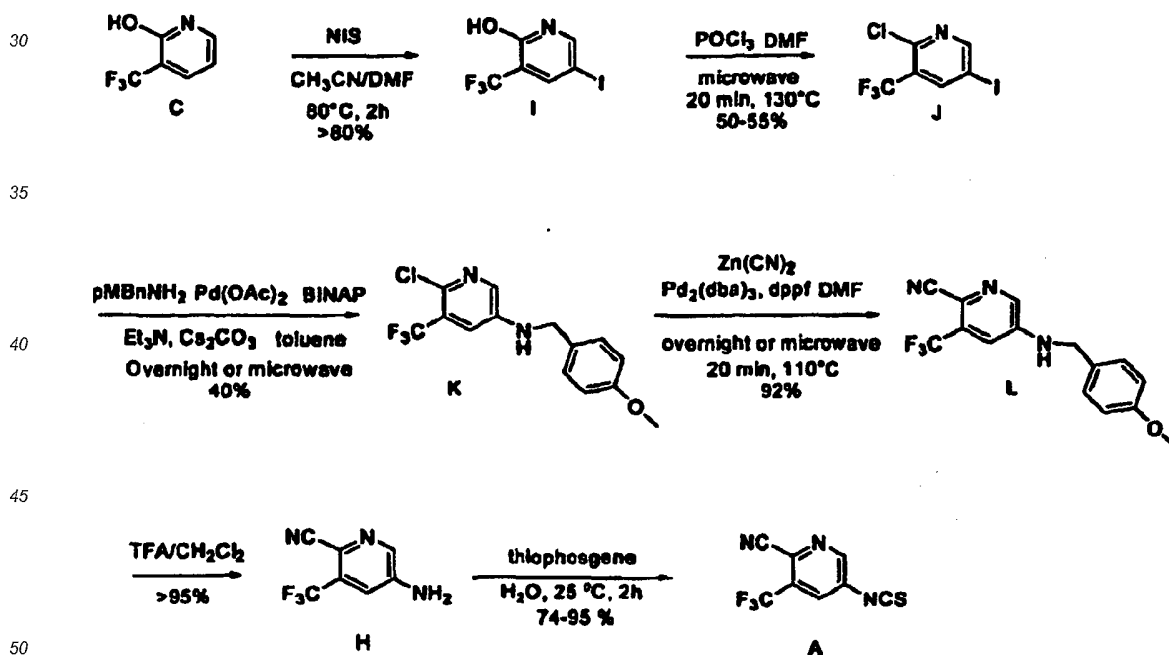
[0063] 5-amino-3-(trifluoromethyl)pyridine-2-carbonitrile **8** is treated as discussed in Example 7 of Scheme 3, above, to obtain 5-isothiocyanato-3-(trifluoromethyl)pyridine-2-carbonitrile **9**.

20 [0064] 5-isothiocyanato-3-(trifluoromethyl)pyridine-2-carbonitrile, **9** is reacted with 4-(1-cyanocyclobutylamino)-2-fluoro-N-methylbenzamide **10** as discussed in Example 8 of Scheme 3, above, to obtain 4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluoro-N-methylbenzamide **11** (**A52**).

Scheme 5: Alternative Synthesis of A52

25 Synthesis of 3-(trifluoromethyl)-5-isothiocyanatopyridine-2-carbonitrile (**A**)

[0065]

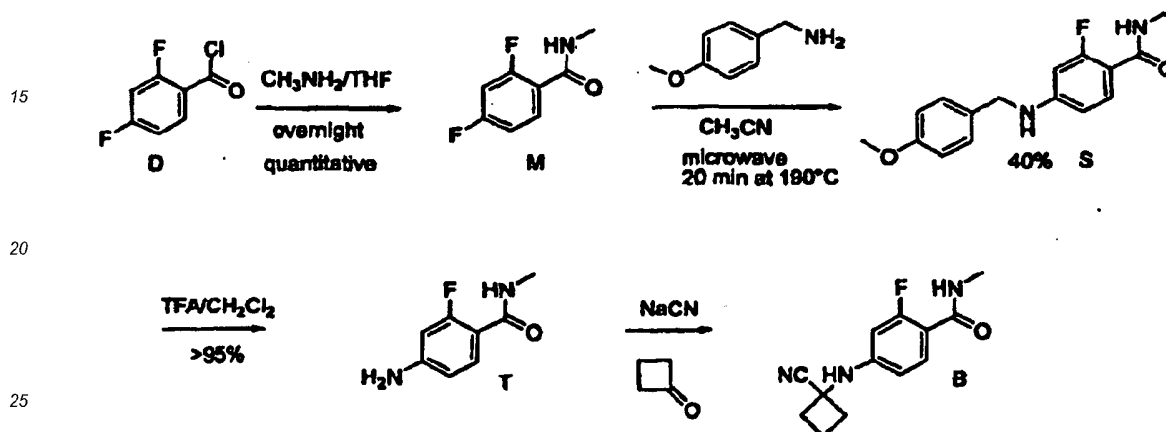


[0066] A solution of 2-hydroxy-3-(trifluoromethyl)pyridine **C** in a mixture of N-iodosuccinimide (NIS), acetonitrile, and dimethylformamide (DMF) is heated at 80°C for 2 hours to produce 2-hydroxy-3-(trifluoromethyl)-5-(iodo)pyridine **I** (greater than 80% yield). The 2-hydroxy-3-(trifluoromethyl)-5-(iodo)pyridine **I** is then mixed with POCl₃ in DMF and heated to 130°C in a microwave for 20 minutes to produce 2-chloro-3-(trifluoromethyl)-5-(iodo)pyridine **J** (yield of 50 to 55%). The 2-chloro-3-(trifluoromethyl)-5-(iodo)pyridine **J** is reacted in a solution of pMBnNH₂, palladium(II) acetate, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), triethylamine, and cesium carbonate in toluene to produce 5-((4-methoxyphenyl)methylamino)-2-chloro-3-(trifluoromethyl)pyridine **K** (yield of 40%). The 5-((4-methoxyphenyl)methylamino)-2-chloro-3-(trifluoromethyl)pyridine **K** is reacted with Zn(CN)₂, Pd₂(dba)₃, dppf, and DMF overnight or in a microwave for 20 minutes at 110°C to produce 5-((4-methoxyphenyl)methylamino)-2-cyano-3-(trifluoromethyl)pyridine **L** (yield of 92%). The 5-((4-methoxyphenyl)methylamino)-2-cyano-3-(trifluoromethyl)pyridine **L** is treated with TFA/CH₂Cl₂ to produce 5-((4-methoxyphenyl)methylamino)-2-cyano-3-(trifluoromethyl)pyridine **H** (>95% yield). The 5-((4-methoxyphenyl)methylamino)-2-cyano-3-(trifluoromethyl)pyridine **H** is treated with thiophosgene in H₂O at 25°C for 2 hours to produce 3-(trifluoromethyl)-5-isothiocyanatopyridine-2-carbonitrile **A** (74-95% yield).

fluoromethyl)pyridine **K** is reacted in a solution of zinc cyanide, tris(dibenzylideneacetone)dipalladium ($\text{Pd}_2(\text{dba})_3$), and 1,1'-bis(diphenylphosphino)ferrocene (dppf) in DMF to provide 5-(4-methoxybenzylamino)-2-cyano-3-(trifluoromethyl)pyridine **K** (yield of 92%). The 5-(4-methoxybenzylamino)-2-cyano-3-(trifluoromethyl)pyridine **K** is reacted in a solution of dichloromethane and trifluoroacetic acid to provide 2-cyano-3-trifluoromethyl-5-(amino)pyridine **H** (yield greater than 95%). The 2-cyano-3-trifluoromethyl-5-(amino)pyridine **H** is reacted with thiophosgene in water at 25 °C for 2 hours to provide 5-isothiocyanato-3-(trifluoromethyl)pyridine-2-carbonitrile **A** (yield of 74% to 95%).

Synthesis of 4-(1-cyanocyclobutylamino)-2-fluoro-N-methylbenzamide intermediate **B**

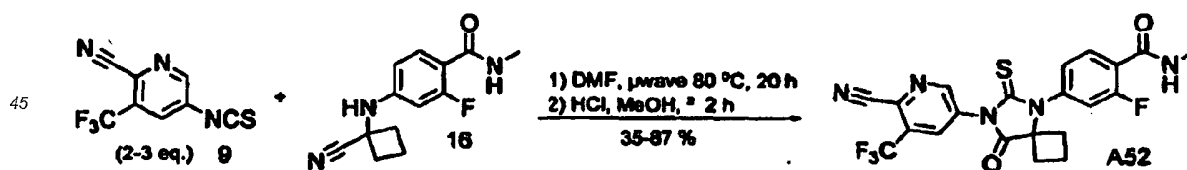
[0067]



[0068] A solution of 2,4-difluorobenzoylchloride **D** in a solution of methylamine and tetrahydrofuran (THF) is allowed to react to produce 2,4-difluoro-N-methylbenzamide **M** (quantitative yield). The 2,4-difluoro-N-methylbenzamide **M** is mixed with in a solution of acetonitrile and 4-methoxy-benzenemethanamine and heated in a microwave for 20 minutes at 190 °C to produce 2-fluoro-4-(4-methoxybenzylamino)-N-methylbenzamide **S** (yield of 40%). The 2-fluoro-4-(4-methoxybenzylamino)-N-methylbenzamide **S** is reacted in a solution of dichloromethane and trifluoroacetic acid to produce 2-fluoro-4-amino-N-methylbenzamide **T** (yield greater than 95%). The 2-fluoro-4-amino-N-methylbenzamide **T** is reacted with a solution of sodium cyanide and cyclobutanone to produce 4-(1-cyanocyclobutylamino)-fluoro-N-methylbenzamide **B**.

Coupling of **A** and **B** to produce 4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluoro-N-methylbenzamide, **A52**

[0069]



[0070] 5-isothiocyanato-3-(trifluoromethyl)pyridine-2-carbonitrile, **9**, **A** is reacted with 4-(1-cyanocyclobutylamino)-2-fluoro-N-methylbenzamide **B** in DMF solution by heating in a microwave at 80 °C for 20 hours. Methanol and hydrochloric acid are then added and the reaction allowed to proceed for 2 hours to produce 4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluoro-N-methylbenzamide, **A52** (yield 35 to 87%).

ACTIVITY

Utility

[0071] The compounds of the present invention modulate the function of the nuclear hormone receptors, particularly

the androgen receptor, and include compounds which are, for example, selective agonists or selective antagonists of the androgen receptor (AR). Thus, the present compounds are useful in the treatment of AR-associated conditions. An "AR-associated condition," as used herein, denotes a condition or disorder which can be treated by modulating the function or activity of an AR in a subject, wherein treatment comprises prevention, partial alleviation or cure of the condition or disorder. Modulation can occur locally, for example, within certain tissues of the subject, or more extensively throughout a subject being treated for such a condition or disorder. Preferably, the compounds with potent antagonistic activity are used for the treatment of androgen related prostate cancer.

Combination

[0072] The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of the invention, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), e.g., an antibiotic or other pharmaceutically active material.

Pharmacological Assay

[0073] The compounds in this invention were identified through screening on hormone sensitive and hormone refractory prostate cancer cells for antagonistic and agonistic activities. The compounds with antagonist activity are potential drugs for the treatment of prostate cancer, both hormone sensitive and hormone refractory.

[0074] The biological activity of the compounds of the invention was measured by secreted levels of prostate specific antigen (PSA). It is well established that PSA levels are indicators of AR activities in prostate cancer. To examine if the compounds affect AR function in a physiological environment, we determined secreted levels of endogenous PSA induced by R3881 in the hormone sensitive (HS) and hormone refractory (HR) cancer cells. HR cells are LNCaP cells engineered to express elevated levels of androgen receptor protein (LNCaP/AR cells), analogous to levels observed in patients with HR cancer who relapse while taking current antiandrogens such as bicalutamide, which acquire agonist properties when AR is highly expressed. LNCaP cells (or LNCaP/AR cells) were maintained in Iscove's medium containing 10% FBS. Five days prior to drug treatment, the cells were grown in Iscove's medium containing 10% CS-FBS to deprive of androgens. The cells were split and grown in Iscove's medium containing 10% CS-FBS with appropriate concentrations of R1881 and the test compounds. After 5 days of incubation, secreted PSA levels were assayed using PSA ELISA kits (American Qualex, San Clemente, CA) (See Fig. 1 and Fig. 3). The MTS assay was also used to examine the growth inhibition of the compounds (See Fig. 2).

Pharmacokinetic data

[0075] The pharmacokinetics of A52 was evaluated in vivo using 8 week-old FVB mice which were purchased from Charles River Laboratories. Mice were divided into groups of three for each time point (See Fig. 4). Two mice were not treated with drug and two other mice were treated with vehicle solution. Each group was treated with 10 mg per kilogram of body weight. The drug was dissolved in a mixture 50 : 10 : 1 : 989 of DMSO : Carboxymethylcellulose : T Tween 80 : H₂O (Vehicle solution) and was administered orally. After drug administration, the animals were euthanized via CO₂ inhalation at different timepoints: 1 min, 5 min, 15 min, 30 min, 2 h, 4 h, 8h, 16 h. Animals were immediately bled after exposure to CO₂ via cardiac puncture (1 ml BD syringe + 27G 5/8 needle).

[0076] The serum samples were analyzed to determine the drug's concentration by the HPLC which (Waters 600 pump, Waters 600 controller and Waters 2487 detector) was equipped with an Alltima C18 column (3 μ , 150 mmx4.6 mm). All RD compounds were detected at 254 nm wave length and bicalutamide was detected at 270 nm wave length.

[0077] The samples for HPLC analysis were prepared according to the following procedure:

- Blood cells were separated from serum by centrifugation.
- To 400 μ l of serum were added 80 μ l of a 10 μ M solution of RD75 in acetonitrile as internal standard and 520 μ l of acetonitrile. Precipitation occurred.
- The mixture was vortexed for 3 minutes and then placed under ultrasound for 30 minutes.
- The solid particles were filtered off or were separated by centrifugation.
- The filtrate was dried under an argon flow to dryness. The sample was reconstructed to 80 μ l with acetonitrile before analyzing by HPLC to determine the drug concentration.
- Standard curve of drug was used to improve accuracy.

In vivo assay

[0078] All animal experiments were performed in compliance with the guidelines of the Animal Research Committee of the University of California at Los Angeles. Animals were bought from Taconic and maintained in a laminar flow tower in a defined flora colony. LNCaP-AR and LNCaP-vector cells were maintained in RPMI medium supplemented with 10% FBS. 10^6 cells in 100 μ l of 1:1 Matrigel to RPMI medium were injected subcutaneously into the flanks of intact or castrated male SCID mice. Tumor size was measured weekly in three dimensions (length x width x depth) using calipers. Mice were randomized to treatment groups when tumor size reached approximately 100 mm³. Drugs were given orally everyday at the dose of 10 mg/kg. (See Fig. 5 and Fig. 6) At a daily dose of 10 mg/kg, compounds A51 and A52 were found to completely retard tumor growth.

[0079] Other doses were also tried. At a daily dose of 1 mg/kg, compounds A51 and A52 were found to have a mild effect. At a daily dose of 25-50 mg/kg, compounds A51 and A52 were found induce some tumor cytotoxicity.

[0080] Prostate cancer cell lines were used for xenografts. For example, a LNCaP xenograft, LAPC4 xenograft, LAPC9 xenograft, and xenografts of the hormone refractory counterparts of these cell lines were made. Other cell lines included V-cap, CWR22 and LAPC4 cell lines. Two cell lines that over express the androgen receptor were generated, LNCaP AR and LAPC4 AR. Prostate cancer progression in these engineered cell lines was found to differ from their parental counterparts. Under androgen ablation, the LNCaP AR and LAPC4 AR lines continued to grow, thus behaving like hormone refractory cells.

[0081] Some of the cell lines were found to not take well in mice in tumor formation when xenografted. However, with LNCaP, 2 million cells gave a 95% take. As few as 1 million cells can be used. These cells required at least 25% Matrigel but no more than 50%. Since high concentrations of cells are required for good tumor take rate, a 27G needle was found to be the smallest appropriate needle.

[0082] The LAPC4 cell line was found to be very difficult to grow in animals. The cells need to be resuspended and filtered through a micron mesh filter, for example, a 40-100 micron mesh filter, because they frequently form large aggregates. Resuspending and running through a filter helps normalize the cell number between each animal and therefore gives more consistent results. LAPC4 requires from about 25%-50% Matrigel, for example, 50% Matrigel, but can be grafted successfully at a lower concentration at 10^5 cells.

[0083] Tumor take in SCID mice was found to be better than in nude mice. For example, the tumor take across individual animal in nude mice was found to be very inconsistent. CB17 SCID mice were used in the study.

[0084] Injections were made subcutaneously on the right flank of the mouse. Slow injection was found to help to produce a round tumor that was easier to measure and could be measured more accurately. In addition, because of the usage of Matrigel, injection of no more than 200 μ l was found appropriate. Injection of 100-200 μ l was found appropriate. Injecting too large a volume created leakage upon needle withdrawal.

[0085] An alternative method to help prevent leakage from needle pullout can be to warm the Matrigel:media:cells filled syringe a couple of seconds to produce a gel-like form. When injecting the gel-like liquid, no leakage should occur. However, allowing the Matrigel to heat for too long a time can cause the suspension to solidify and become uninjectable.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

[0086] The compounds of the invention are useful as pharmaceutical compositions prepared with a therapeutically effective amount of a compound of the invention, as defined herein, and a pharmaceutically acceptable carrier or diluent.

[0087] The compounds of the invention can be formulated as pharmaceutical compositions and administered to a subject in need of treatment, for example a mammal, such as a human patient, in a variety of forms adapted to the chosen route of administration, for example, orally, nasally, intraperitoneally, or parenterally, by intravenous, intramuscular, topical or subcutaneous routes, or by injection into tissue. Such compositions and preparations should contain at least 0.01% of a compound or compounds of the invention. The percentage of the compositions and preparations may, of course, be varied and may, for example, be between about 0.05% to about 2% of the weight of a given unit dosage form. The amount of compounds in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[0088] Thus, compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier, or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The compounds may be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% of a compound or compounds of the invention. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of compounds in such

therapeutically useful compositions is such that an effective dosage level will be obtained.

[0089] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose, or aspartame, or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac, sugar, and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the compounds of the invention may be incorporated into sustained-release preparations and devices. For example, the compounds may be incorporated into time release capsules, time release tablets, and time release pills.

[0090] The compounds of the invention may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the compounds can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

[0091] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the compounds of the invention which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid, and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions, or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers, or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0092] Sterile injectable solutions are prepared by incorporating the compounds of the invention in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[0093] For topical administration, the compounds of the invention may be applied in pure form. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

[0094] Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina, and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols, or glycols or water/alcohol/glycol blends, in which the compounds of the invention can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

[0095] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses, or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[0096] Examples of useful dermatological compositions which can be used to deliver the compounds of the present invention to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157), and Wortzman (U.S. Pat. No. 4,820,508), all of which are hereby incorporated by reference.

[0097] Useful dosages of the compounds A51 and A52 can be determined by comparing their in vitro activity, and by comparing their in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice and other animals to humans are known to the art; for example, see U.S. Pat. No. 4,938,949, which is hereby incorporated by reference.

[0098] For example, the concentration of the compounds in a liquid composition, such as a lotion, can be from about 0.1 to about 25% by weight, or from about 0.5 to about 10% by weight. The concentration in a semi-solid or solid

composition such as a gel or a powder can be from about 0.1 to about 5% by weight, or from about 0.5 to about 2.5% by weight.

[0099] The amount of the compounds of the invention required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[0100] Effective dosages and routes of administration of agents of the invention are conventional. The exact amount (effective dose) of the agent will vary from subject to subject, depending on, for example, the species, age, weight, and general or clinical condition of the subject, the severity or mechanism of any disorder being treated, the particular agent or vehicle used, the method and scheduling of administration, and the like. A therapeutically effective dose can be determined empirically, by conventional procedures known to those of skill in the art. See, e.g., *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, eds., Macmillan Publishing Co., New York. For example, an effective dose can be estimated initially either in cell culture assays or in suitable animal models. The animal model may also be used to determine the appropriate concentration ranges and routes of administration. Such information can then be used to determine useful doses and routes for administration in humans. A therapeutic dose can also be selected by analogy to dosages for comparable therapeutic agents.

[0101] The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (e.g., the subject, the disease, the disease state involved, and whether the treatment is prophylactic). Treatment may involve daily or multi-daily doses of compound(s) over a period of a few days to months, or even years.

[0102] In general, however, a suitable dose will be in the range of from about 0.01 to about 500 mg/kg per day, e.g., from about 0.1 to about 500 mg/kg of body weight per day, such as from about 0.1 to about 100 mg per kilogram body weight of the recipient per day. For example, a suitable dose may be about 1 mg/kg, 10 mg/kg, or 50 mg/kg of body weight per day.

[0103] The compounds of the invention are conveniently administered in unit dosage form; for example, containing from about 0.0005 to about 500 mg, from about 0.01 to about 50 mg, from about 0.05 to about 10 mg, or about 5 mg of active ingredient per unit dosage form.

[0104] The compounds of the invention can be administered to achieve peak plasma concentrations of, for example, from about 0.5 to about 75 μ M, about 1 to 50 μ M, about 2 to about 30 μ M, or about 5 to about 25 μ M. Exemplary desirable plasma concentrations include at least or no more than 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 or 200 μ M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the compounds of the present invention, optionally in saline, or orally administered as a bolus containing about 1-1000 mg of the compounds. Desirable blood levels may be maintained by continuous infusion to provide from about 0.0005 to about 25 mg per kg body weight per hour, for example at least or no more than 0.0005, 0.005, 0.05, 0.5, 5, or 25 mg/kg/hr. Alternatively, such levels can be obtained by intermittent infusions containing from about 0.002 to about 100 mg per kg body weight, for example, at least or no more than 0.002, 0.02, 0.2, 2, 20, 50, or 100 mg of the compounds per kg of body weight.

[0105] The compounds of the invention may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator.

EXAMPLE: INTRAVENOUS FORMULATION

[0106] A compound A51 or A52 can be in a formulation suitable for intravenous dosing. In an embodiment, the compound is dissolved in from about 10% to about 25% dimethylsulfoxide (DMSO). 1X phosphate buffered saline (PBS) is then mixed into the solution as the balance, and the solution is sonicated with a water bath sonicator until it is homogeneous.

[0107] At a compound concentration of 1.5 mg/mL, 5 minutes of sonication may be sufficient to dissolve the compound. At a compound concentration of 2 mg/ml, more than 5 minutes of sonication may be required to dissolve the compound and a polyethylene glycol can be added to keep the compound in suspension. For example, 5 to 40% PEG-400 (a polyethylene glycol), such as, 5-10% PEG-400, can be added.

[0108] The above solution, including either A51 or A52, was found to be stable at room temperature for at least a week.

[0109] Before administration, the above solution should be sonicated for a few minutes. A maximum appropriate administration volume for mice was found to be 0.2 mL.

[0110] When administered to mice, hardening of the skin and skin irritation around the injection site was observed, and this was attributed to the use of DMSO. Although compounds A51 and A52 are soluble in ethanol, ethanol was found to reduce the stability of the compounds in vivo.

[0111] Over a period of 2 weeks following administration of the above solution, mice were observed to lose 15% of body weight.

EXAMPLE: ORAL FORMULATION

[0112] A compound A51 or A52 can be in a formulation suitable for oral administration. In an embodiment, the compound is dissolved in 100% DMSO.

[0113] Additional chemicals can be added, such as a carboxymethylcellulose, a polysorbate, or water. For example, the components of the solution other than A51 or A52 can be present at concentrations of from about 10% to about 20% DMSO, from about 1% to about 2% carboxymethylcellulose (CMC), and 0.1% Tween 80 (a polysorbate), with the balance being water. The concentration of compound A51 or A52 in the oral foundation can be about 1.5 mg/mL. The solution is mechanically homogenized for at least 30 seconds. The compound A51 or A52 was found to stay in suspension for only a couple of hours and, therefore, the oral formulation must be administered within a couple of hours of preparation.

[0114] When more than 2% carboxymethylcellulose (CMC) was included in the solution, the formulation was found to be very viscous, so that when administered to a test animal with a gavage syringe, much of the formulation was left behind on the walls of the syringe, preventing accurate drug administration. A solution of 10% DMSO that included CMC and Tween 80 was found to keep the compound in suspension when mechanical homogenization was applied. That is, more than 10% DMSO was not required. A minimum of DMSO should be used, because it was found to irritate the mice, and was associated with a loss of up to 10% of the bodyweight of the mice over a period of 2 weeks following administration.

[0115] A maximum appropriate administration volume for mice was found to be 0.2 mL.

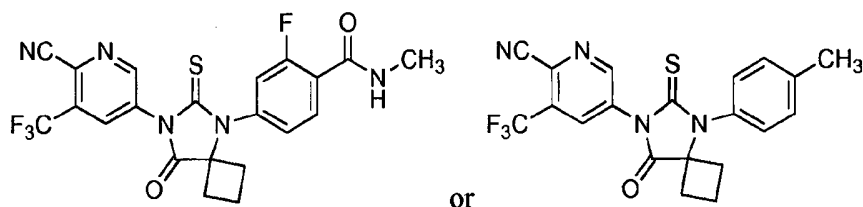
[0116] The half life of the compound was found to be longer when it was administered intravenously than when it was administered orally. However, daily oral dosing resulted in an acceptable steady state serum concentration of the compound, comparable to the steady state concentration seen with bicalutamide. Oral administration may be more convenient than intravenous administration.

[0117] Compounds A51 and A52 have a beneficial effect on tumors in an in vivo assay administered as described.

[0118] The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. All examples presented are representative and non-limiting. The above-described embodiments of the invention may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims, the invention may be practiced otherwise than as specifically described.

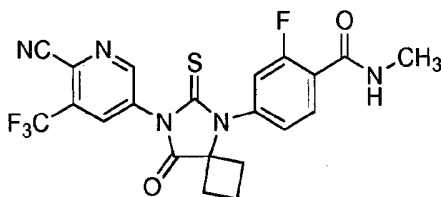
Claims

1. A compound having the formula:



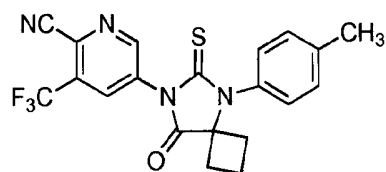
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 having the formula



3. The compound of claim 1 having the formula

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4. A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof for use as a medicament.

5. A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof for use in:

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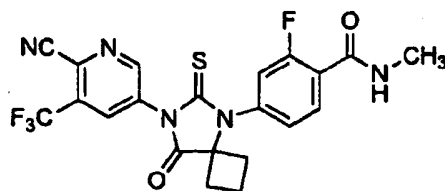
- (a) the treatment of a disease or disorder related to nuclear receptor activity;
- (b) the treatment of a hyperproliferative disorder;
- (c) the treatment of prostate cancer;
- (d) the treatment of hormone sensitive prostate cancer; or
- (e) the treatment of hormone refractory prostate cancer in a mammal.

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6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or adjuvant.

7. The pharmaceutical composition of claim 6, wherein the compound is:

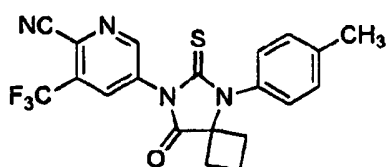
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8. The pharmaceutical composition of claim 6, wherein the compound is:

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9. The pharmaceutical composition of any one of claims 6 to 8, which is in a form that is suitable for administration to a mammal systemically.

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10. The pharmaceutical composition of any one of claims 6 to 8, wherein the pharmaceutical composition is in a form that is suitable for administration by intravenous injection, by injection into tissue, intraperitoneally, orally or nasally.

11. The pharmaceutical composition of any one of claims 6 to 8, wherein the pharmaceutical composition is a solution, dispersion, suspension, powder, capsule, tablet or a pill.

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12. A pharmaceutical composition according to any one of claims 6 to 11 for use as a medicament.

13. A pharmaceutical composition according to any one of claims 6 to 11 for use in:

- (a) the treatment of a disease or disorder related to nuclear receptor activity;

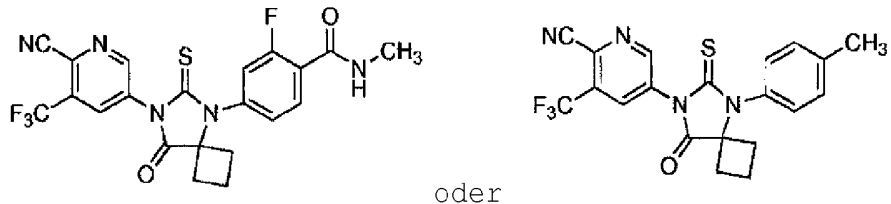
- (b) the treatment of a hyperproliferative disorder;
- (c) the treatment of prostate cancer;
- (d) the treatment of hormone sensitive prostate cancer; or
- (e) the treatment of hormone refractory prostate cancer in a mammal.

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Patentansprüche

1. Verbindung mit der Formel:

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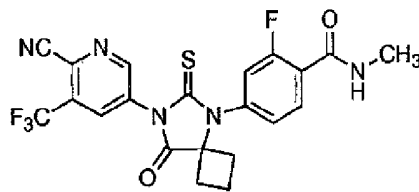
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oder ein pharmazeutisch annehmbares Salz davon.

2. Verbindung gemäß Anspruch 1 mit der Formel

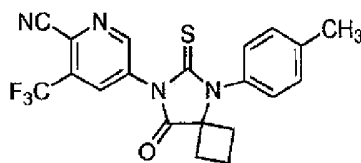
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3. Verbindung gemäß Anspruch 1 mit der Formel

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4. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 3, oder ein pharmazeutisch annehmbares Salz davon zur Verwendung als ein Medikament.

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5. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 3, oder ein pharmazeutisch annehmbares Salz davon zur Verwendung zur:

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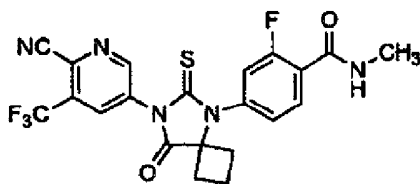
- (a) Behandlung einer Erkrankung oder Störung, die mit Kern-Rezeptoraktivität in Beziehung steht;
- (b) Behandlung einer hyperproliferativen Störung;
- (c) Behandlung von Prostatakrebs;
- (d) Behandlung von Hormon-sensitivem Prostatakrebs; oder
- (e) Behandlung von Hormon-refraktärem Prostatakrebs bei einem Säuger.

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6. Pharmazeutische Zusammensetzung, die eine therapeutisch wirksame Menge einer Verbindung gemäß einem beliebigen der Ansprüche 1 bis 3 oder eines pharmazeutisch annehmbaren Salzes davon und einen/ein pharmazeutisch annehmbaren/annehmbares Träger, Verdünnungsmittel oder Adjuvans umfasst.

7. Pharmazeutische Zusammensetzung gemäß Anspruch 6, wobei die Verbindung:

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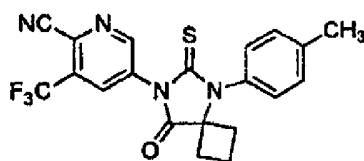


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ist.

8. Pharmazeutische Zusammensetzung gemäß Anspruch 6, wobei die Verbindung:

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ist.

9. Pharmazeutische Zusammensetzung gemäß einem beliebigen der Ansprüche 6 bis 8, die in einer Form ist, die geeignet zur systemischen Verabreichung an einen Säuger ist.

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10. Pharmazeutische Zusammensetzung gemäß einem beliebigen der Ansprüche 6 bis 8, wobei die pharmazeutische Zusammensetzung in einer Form ist, die geeignet zur Verabreichung durch intravenöse Injektion, durch Injektion in Gewebe, zur intraperitonealen, oralen oder nasalen Verabreichung, ist.

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11. Pharmazeutische Zusammensetzung gemäß einem beliebigen der Ansprüche 6 bis 8, wobei die pharmazeutische Zusammensetzung eine Lösung, Dispersion, Suspension, ein Pulver, eine Kapsel, eine Tablette oder eine Pille ist.

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12. Pharmazeutische Zusammensetzung gemäß einem beliebigen der Ansprüche 6 bis 11 zur Verwendung als ein Medikament.

13. Pharmazeutische Zusammensetzung gemäß einem beliebigen der Ansprüche 6 bis 11 zur Verwendung zur:

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- (a) Behandlung einer Erkrankung oder Störung, die mit Kern-Rezeptoraktivität in Beziehung steht;
- (b) Behandlung einer hyperproliferativen Störung;
- (c) Behandlung von Prostatakrebs;
- (d) Behandlung von Hormon-sensitivem Prostatakrebs; oder
- (e) Behandlung von Hormon-refraktärem Prostatakrebs bei einem Säuger.

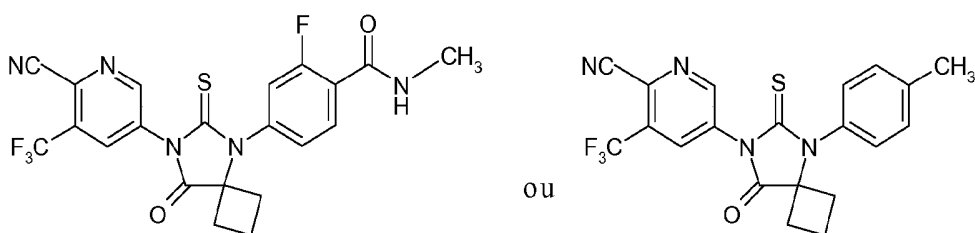
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Revendications

1. Composé de formule

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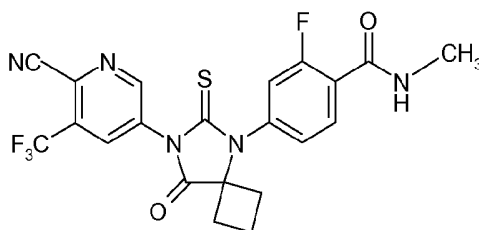
ou

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ou sel pharmacologiquement admissible de l'un de ces composés.

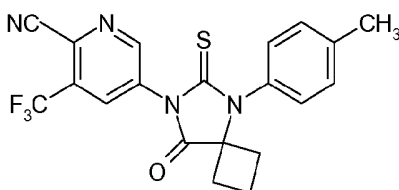
2. Composé conforme à la revendication 1, de formule

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- 25 3. Composé conforme à la revendication 1, de formule



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4. Composé conforme à l'une des revendications 1 à 3, ou sel pharmacologiquement admissible de l'un de ces composés, pour utilisation en tant que médicament.

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5. Composé conforme à l'une des revendications 1 à 3, ou sel pharmacologiquement admissible de l'un de ces composés, pour utilisation :

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- a) dans le traitement d'une maladie ou d'un trouble en relation avec l'activité d'un récepteur nucléaire,
- b) dans le traitement d'un trouble hyperprolifératif,
- c) dans le traitement d'un cancer de la prostate,
- d) dans le traitement d'un cancer de la prostate hormono-sensible,
- e) ou dans le traitement d'un cancer de la prostate hormono-réfractaire, chez un mammifère.

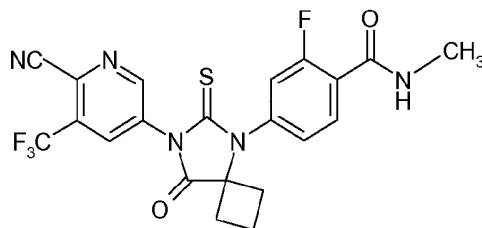
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6. Composition pharmaceutique comprenant, en une quantité à effet thérapeutique, un composé conforme à l'une des revendications 1 à 3, ou un sel pharmacologiquement admissible de l'un de ces composés, et un véhicule, adjuvant ou diluant pharmacologiquement admissible.

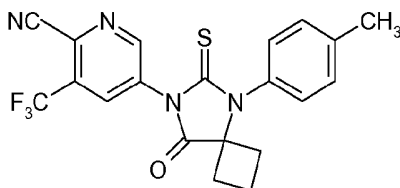
7. Composition pharmaceutique conforme à la revendication 6, dans laquelle le composé est celui de formule

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8. Composition pharmaceutique conforme à la revendication 6, dans laquelle le composé est celui de formule



9. Composition pharmaceutique conforme à l'une des revendications 6 à 8, qui se présente sous une forme appropriée pour être administrée par voie systémique à un mammifère.

- 25 10. Composition pharmaceutique conforme à l'une des revendications 6 à 8, laquelle composition pharmaceutique se présente sous une forme appropriée pour être administrée par injection intraveineuse, par injection dans un tissu, ou par voie intrapéritonéale, orale ou nasale.

- 30 11. Composition pharmaceutique conforme à l'une des revendications 6 à 8, laquelle composition pharmaceutique est une solution, une dispersion, une suspension, une poudre, une capsule, un comprimé ou une pilule.

12. Composition pharmaceutique conforme à l'une des revendications 6 à 11, pour utilisation en tant que médicament.

- 35 13. Composition pharmaceutique conforme à l'une des revendications 6 à 11, pour utilisation

- 40 a) dans le traitement d'une maladie ou d'un trouble en relation avec l'activité d'un récepteur nucléaire,
b) dans le traitement d'un trouble hyperprolifératif,
c) dans le traitement d'un cancer de la prostate,
d) dans le traitement d'un cancer de la prostate hormono-sensible,
e) ou dans le traitement d'un cancer de la prostate hormono-réfractaire,
chez un mammifère.

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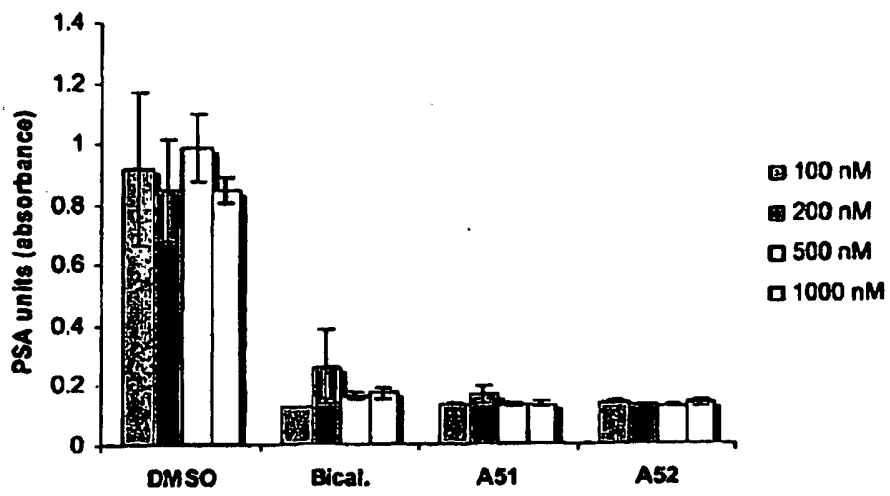


FIG. 1

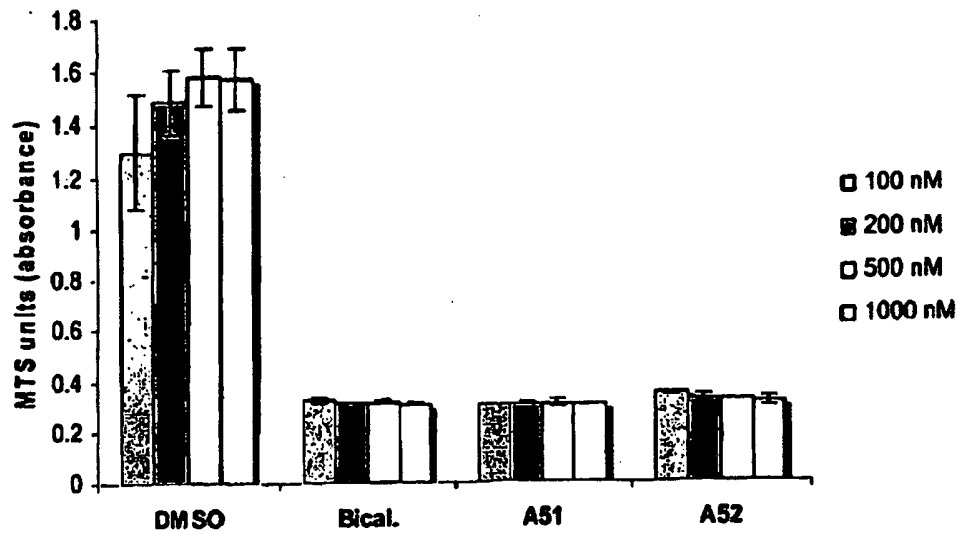


FIG. 2

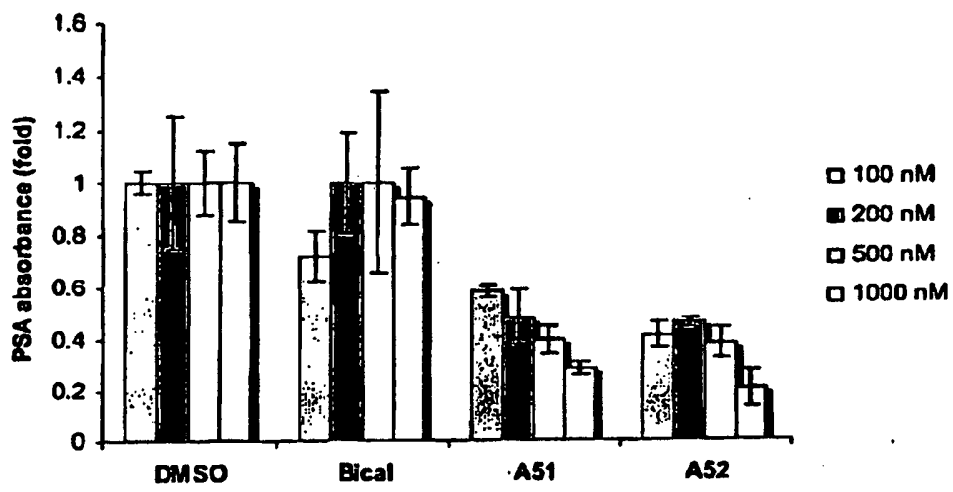


FIG. 3

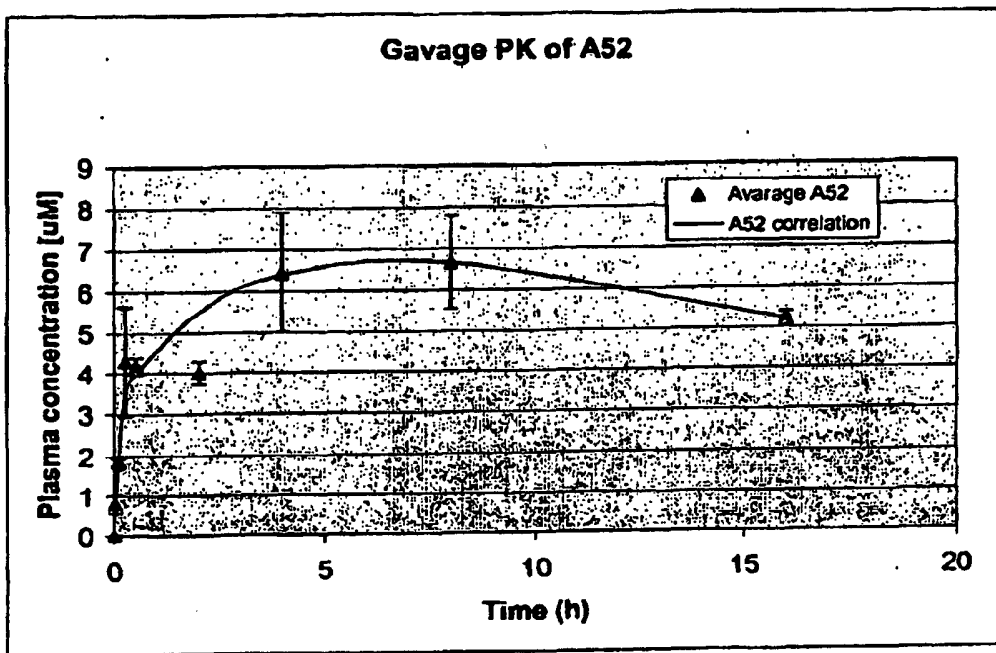


FIG. 4

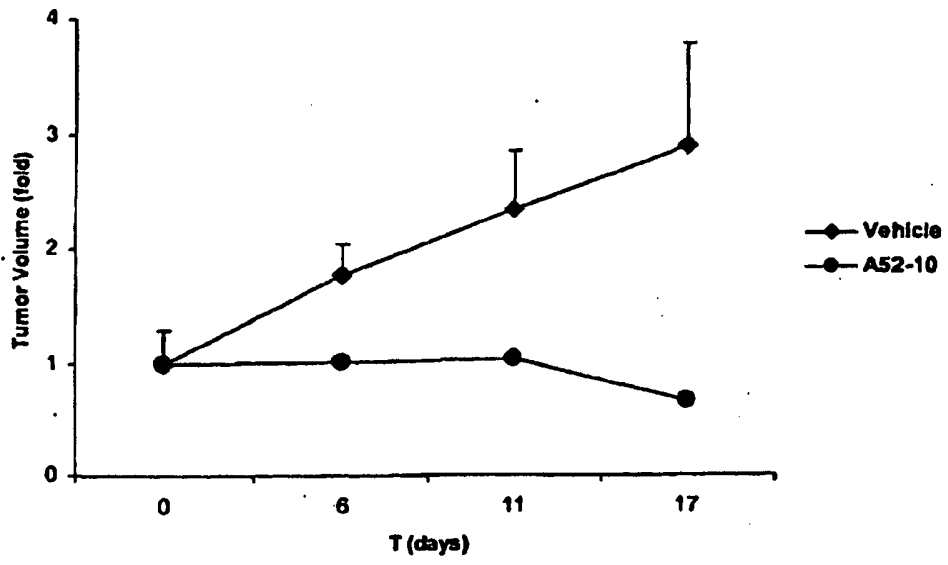


FIG. 5

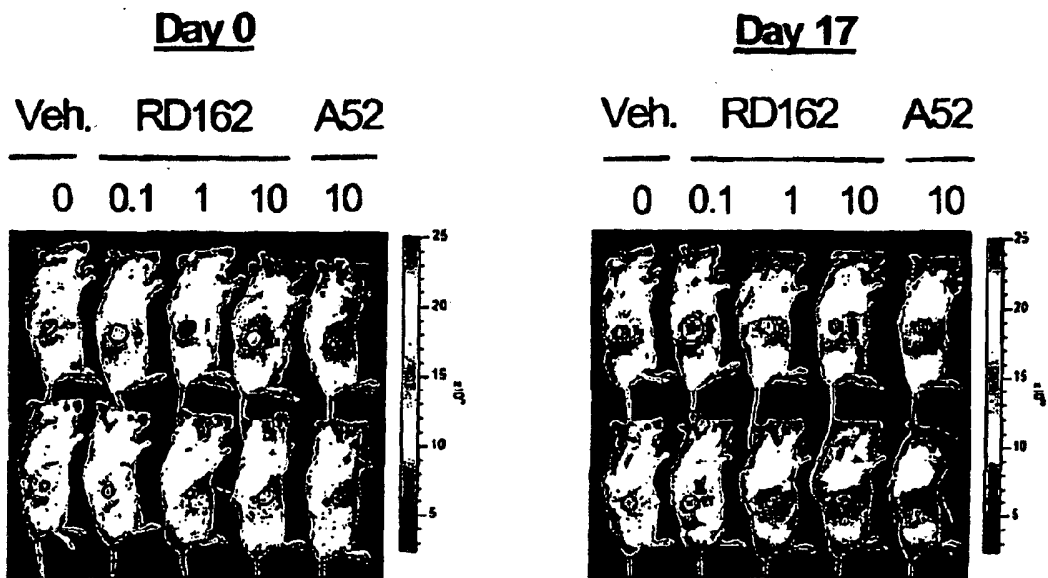


FIG. 6

REFERENCES CITED IN THE DESCRIPTION

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