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(54) Title: METHODS AND COMPOSITIONS FOR TREATING CANCER

(57) Abstract: Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α-hydroxylase/$C_{17,\ 20}$-lyase inhibitor, such as abiraterone acetate (i.e., 3β-acetoxy-17-(3-pyridyl) androsta-5, 16-diene), in combination with at least one additional therapeutic agent such as an anti¬ cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α- hydroxylase/$C_{17,\ 20}$-lyase inhibitor, and at least one additional therapeutic agent, such as an anti-cancer agent or a steroid.

METHODS AND COMPOSITIONS FOR TREATING CANCER

FIELD OF THE INVENTION

[0001] Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate (*i.e.*, 3β-acetoxy-17-(3-pyridyl) androsta-5, 16-diene), in combination with at least one additional therapeutic agent, such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, and at least one additional therapeutic agent such as an anti-cancer agent or a steroid, *e.g.*, a corticosteroid or, more specifically, a glucocorticoid.

BACKGROUND

[0002] The number of people diagnosed with cancer has significantly increased. Of special interest are individuals diagnosed with androgen-dependent disorders, such as prostate cancer, and estrogen-dependent disorders, such as breast cancer since such diagnoses are increasing in number at an alarming rate.

[0003] Prostate cancer is currently the most common non-skin cancer and the second leading cause of cancer-related death in men after lung cancer. The primary course of treatment for patients diagnosed with organ-confined prostate cancer is usually prostatectomy or radiotherapy. Not only are these treatments highly invasive and have undesirable side effects, such localized treatments are not effective on prostate cancer after it has metastasized. Moreover, a large percent of individuals who receive localized treatments will suffer from recurring cancer.

[0004] Additionally, breast cancer incidence in women has increased from one out of every 20 women in 1960 to one out of every eight women in 2005. Moreover, it is the most common cancer among white and African-American women. Similar to treating prostate cancer, most options for women diagnosed with breast cancer are highly invasive and have significant side-effects. Such treatments include surgery, radiation and chemotherapy.

[0005] Hormone therapy is another treatment option for individuals diagnosed with prostate or breast cancer. Hormone therapy is a form of systemic treatment for prostate or breast cancer wherein hormone ablation agents are used to suppress the production or block

the effects of hormones, such as estrogen and progesterone in the body, which are believed to promote the growth of breast cancer, as well as testosterone and dihydrotestosterone, which are believed to promote the growth of prostate cancer. Moreover, hormone therapy is less invasive than surgery and does not have many of the side effects associated with chemotherapy or radiation. Hormone therapy can also be used by itself or in addition to localized therapy and has shown to be effective in individuals whose cancer has metastasized.

[0006] Even though hormone therapy is less invasive and can be used on more advanced stages of cancer, some individuals administered current hormone therapy treatments may not show a significant response or may not show any response at all to such treatments. Additionally, some patients treated with current hormone therapy treatments may also suffer from relapsing or recurring cancer. Currently, such refractory cancer patients are left with very few treatment options.

[0007] Despite the progress made in the treatment of cancer, there remains a need for more effective ways to treat cancer such as, but not limited to, prostate cancer and breast cancer. Additionally, there is a need for effective anti-cancer treatment options for patients who are not responding to current anti-cancer treatments. Also, there is a need for effective anti-cancer treatment options for patients whose cancer has recurred.

SUMMARY OF THE INVENTION

[0008] Described herein are methods for treating a cancer in which a therapeutically effective amount of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate (*i.e.* 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene), is administered to a patient, *e.g.*, a patient in need thereof, in combination with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent or steroid. Such methods can also provide an effective treatment for individuals with a refractory cancer, including individuals who are currently undergoing a cancer treatment. Therefore, in certain embodiments, the method is directed to treating a refractory cancer in a patient, in which a therapeutically effective amount of 17α-hydroxylase/$C_{17,20}$-lyase inhibitor is administered to a patient currently receiving an anti-cancer agent.

[0009] For example, in certain embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about

100 mg/kg/day of abiraterone acetate and an amount of about 0.1 mg/m^2 to about 20 mg/m^2 of mitoxantrone.

[0010] In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m^2 to about 175 mg/m^2 of paclitaxel.

[0011] In still other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m^2 to about 100 mg/m^2 of docetaxel.

[0012] Furthermore, described herein is a method for the treatment of a cancer in a mammal comprising administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate; and an amount of about 0.01 mg to about 200 mg of leuprolide, wherein the leuprolide is administered over a period of about 3 days to about 12 months.

[0013] In other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of goserelin, wherein the goserelin is administered over a period of about 28 days to about 3 months.

[0014] Additionally, in another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of triptorelin, wherein the triptorelin is administered over a period of about 1 month.

[0015] The method for the treatment of a cancer in a mammal can also comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 μg/day to about 500 μg/day of seocalcitol, such as about 100 μg/day of seocalcitol.

[0016] Also, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

[0017] In yet another embodiment, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100

mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

[0018] Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone.

[0019] Also described herein are compositions for the treatment of cancer that comprise a combination of a therapeutically effective amount of at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and a therapeutically effective amount of at least one additional anti-cancer agent, such as, but not limited to, mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including, but not limited to, hydrocortisone, prednisone, or dexamethasone.

[0020] Finally, single unit dosage forms comprising abiraterone acetate and a glucocorticoid, optionally with carriers, diluents or excipients, are contemplated. Also, kits comprising at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and an additional anti cancer agent or steroid are contemplated. For example, the kit may include a vial containing abiraterone acetate and another vial containing a glucocorticoid.

Definitions

[0021] As used herein and unless otherwise defined the word "cancer," refers to the growth, division or proliferation of abnormal cells in the body. Cancers that can be treated with the methods and the compositions described herein include, but are not limited to, prostate cancer, breast cancer, adrenal cancer, leukemia, lymphoma, myeloma, Waldenström's macroglobulinemia, monoclonal gammopathy, benign monoclonal gammopathy, heavy chain disease, bone and connective tissue sarcoma, brain tumors, thyroid cancer, pancreatic cancer, pituitary cancer, eye cancer, vaginal cancer, vulvar cancer, cervical cancer, uterine cancer, ovarian cancer, esophageal cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, lung cancer, testicular cancer, penal cancer, oral cancer, skin cancer, kidney cancers, Wilms' tumor and bladder cancer.

[0022] As used herein, and unless otherwise defined, the terms "treat," "treating" and "treatment" include the eradication, removal, modification, management or control of a

tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.

[0023] As used herein, and unless otherwise defined, the term "patient" means an animal, including but not limited to an animal such as a human, monkey, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, or guinea pig. In one embodiment, the patient is a mammal and in another embodiment the patient is a human. In certain embodiments, the patient can be an adult male or female. In some embodiments, the patient is a male of age about 30 years to about 85 years. In other embodiments, the patient is a female of age about 30 years to about 85 years. In a particular embodiment, the patient has or is susceptible to having (*e.g.*, through genetic or environmental factors) cancer. In a further embodiment, the patient has or is susceptible to having (*e.g.*, through genetic or environmental factors) a tumor. In other embodiments, the patient can be castrated or non-castrated.

[0024] The term "17α-hydroxylase/$C_{17,20}$-lyase inhibitor" as used herein refers to an inhibitor of 17α-hydroxylase/$C_{17,20}$-lyase, (which is an enzyme in testosterone synthesis), an analog thereof, derivative thereof, metabolite thereof or pharmaceutically acceptable salt thereof. Also, unless otherwise noted, reference to a particular 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can include analogs, derivatives, metabolites or pharmaceutically acceptable salts of such particular 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0025] The term "anti-cancer agent" as used herein refers to any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells. It should be noted that even though throughout this specification and in the claims the phrase "anti-cancer agent" is written as a singular noun, for example; "an anti-cancer agent" or "the anti-cancer agent," the phrase "anti-cancer agent" should not be interpreted as being limited to the inclusion of a single anti-cancer agent.

[0026] As used herein, and unless otherwise defined, the phrase "therapeutically effective amount" when used in connection with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor or therapeutic agent means an amount of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor or therapeutic agent effective for treating a disease or disorder disclosed herein, such as cancer.

[0027] As used herein and unless otherwise defined the phrase "refractory cancer," means cancer that is not responding to an anti-cancer treatment or cancer that is not

responding sufficiently to an anti-cancer treatment. Refractory cancer can also include recurring or relapsing cancer.

[0028] As used herein and unless otherwise defined the phrase "refractory patient," means a patient who has refractory cancer.

[0029] As used herein and unless otherwise defined the phrase "relapse cancer," means cancer that was at one time responsive to an anti-cancer treatment but has become no longer responsive to such treatment or is no longer responding sufficiently to such treatment.

[0030] As used herein and unless otherwise defined the phrase "recurring cancer," means cancer that has returned after a patient has been earlier diagnosed with cancer, under gone treatment or had been previously diagnosed as cancer-free.

[0031] As used herein and unless otherwise defined the term "derivative" refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound. The derivative may retain or improve the pharmacological activity of the compound from which it is derived.

[0032] As used herein and unless otherwise defined the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

[0033] As used herein and unless otherwise defined the phrase "pharmaceutically acceptable salt" refers to any salt of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor which retains the biological effectiveness of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor. Examples of pharmaceutically acceptable salts include, but are not limited to, acetates, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartarates, alkanesulfonates (*e.g.* methane-sulfonate or mesylate), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-

sulfonates, and mandelates. Several of the officially approved salts are listed in Remington: The Science and Practice of Pharmacy, Mack Publ. Co., Easton.

DETAILED DESCRIPTION OF THE INVENTION

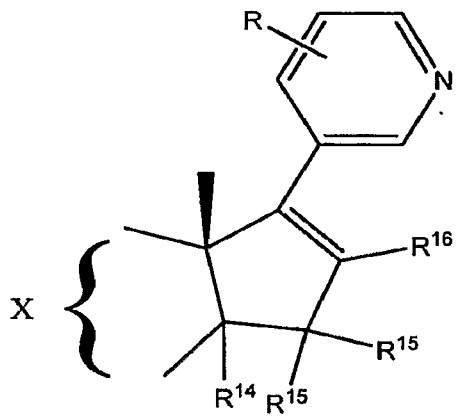
[0034] The methods described herein for treating cancer comprise administering to a mammal, preferably a human, a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor in addition to at least one therapeutic agent, such as an anti-cancer agent or steroid, particularly a glucocorticoid. The compositions described herein comprise a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and at least one additional therapeutic agent, such as an anti-cancer agent or steroid, particularly a corticosteroid or glucocorticoid. Other anti-cancer treatments such as, administration of yet another anti-cancer agent, radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy, can be used with the methods and compositions.

17α-hydroxylase/$C_{17,20}$-lyase Inhibitors

[0035] 17α-hydroxylase/$C_{17,20}$-lyase inhibitors have been shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer respectively, as described in United States Patent No. 5,604,213 to Barrie *et al.*, which is herein incorporated by reference in its entirety.

[0036] In certain embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can be 17-(3-pyridyl)androsta-5,16-dien-3β-ol; 17-(3-pyridyl)androsta-3,5,16-triene; 17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol; 17-(3-pyridyl)-5α-androst-16-en-3α-ol; 17-(3-pyridyl)-5α -androst-16-en-3-one; 17-(3-pyridyl)-androsta-4,16-diene-3,11-dione; 17-(3-pyridyl)-androsta-3,5,16-trien-3-ol; 6α-and 6β-fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)androsta-4,16-dien-3,6-dione; 3α-trifluoromethyl-17-(3-pyridyl)androst-16-en-3β-ol or their acid addition salts and 3-esters as well as metabolites, analogs, derivatives or a pharmaceutically acceptable salt thereof.

[0037] In certain embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can have the structure of formula (I):



(I)

wherein X represents the residue of the A, B and C rings of a steroid which can be, without limitation, androstan-3α- or 3β-ol; androst-5-en-3α- or 3β-ol; androst-4-en-3-one; androst-2-ene; androst-4-ene; androst-5-ene; androsta-5,7-dien-3α or 3β-ol ; androsta-1,4-dien-3-one; androsta-3,5-diene; androsta-3,5-diene-3-ol; estra-1,3,5[10]-triene; estra-1,3,5[10]-trien-3-ol; 5α -androstan-3-one; androst-4-ene-3,11-dione; 6-fluoroandrost-4-ene-3-one; or androstan-4-ene-3,6-dione; each of which, where structurally permissible, can be further derivatized in one or more of the following ways, including, but not limited to, to form 3-esters; to have one or more carbon or carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions; as 3-oximes; as 3-methylenes; as 3-carboxylates; as 3-nitriles; as 3-nitros; as 3-desoxy derivatives; to have one or more hydroxy, halo, C_{1-4} -alkyl, trifluoro-methyl, C_{1-4} -alkoxy, C_{1-4} -alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring; or to be 19-nor;

R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

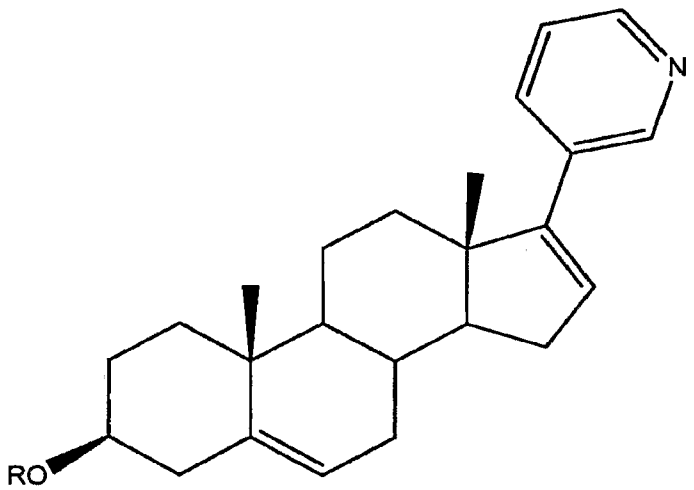
R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts, but excluding 3β-acetoxy-17-(3-pyridyl)androsta-5,14,16-triene, 3β,15α- and 3β,15β-diacetoxy-17-(3-pyridyl)androsta-5,16-diene and 3β-methoxy-17-(3-pyridyl-5α-androst-16-ene.

Suitable inhibitors also include metabolites, derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

[0038] In another embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can have the structure of formula (I):

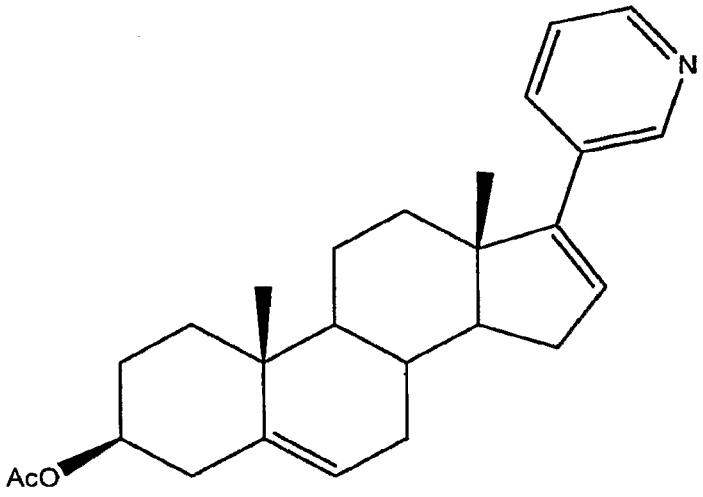


(I)

wherein R represents hydrogen or a lower acyl group having 1 to 4 carbons. Suitable inhibitors also include derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

[0039] In still another embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can be a 3β-alkanoyloxy-17-(3-pyridyl) androsta-5, 16-diene in which the alkanoyloxy group has from 2 to 4 carbon atoms.

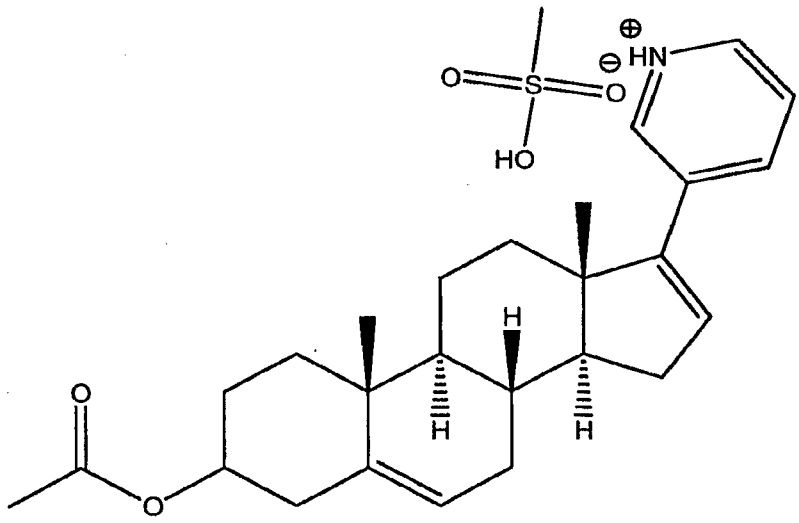
[0040] In a preferred embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises abiraterone acetate or 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene which has the following structural formula:



(II)

and pharmaceutically acceptable salts thereof.

[0041] Preferred salts of abiraterone acetate and methods of making such salts are also disclosed in United States Provisional Application No. 60/603,559 to Hunt, which is incorporated by reference in its entirety. Preferred salts include, but are not limited to, acetates, citrates, lactates, alkanesulfonates (e.g. methane-sulfonate or mesylate) and tartarates. Of special interest is the abiraterone acetate mesylate salt (*i.e.* 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene mesylate salt) which has the following structural formula:



(III)

[0042] The 17α-hydroxylase/$C_{17,20}$-lyase inhibitors can be made according to any method known to one skilled in the art. For example, such inhibitors can be synthesized according to the method disclosed in United States Patent Nos. 5,604,213 and 5,618,807 to Barrie *et al.*, herein incorporated by reference. Another method of making 17α-

hydroxylase/$C_{17,20}$-lyase inhibitors is disclosed in United States provisional application 60/603,558 to Bury, herein incorporated by reference.

[0043] The amount of 17α-hydroxylase/$C_{17,20}$-lyase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer, whether the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor is administered alone or in combination with an additional anti-cancer treatment, such as an additional anti-cancer agent.

Additional Therapeutic Agents

[0044] Suitable compounds that can be used in addition to 17α-hydroxylase/$C_{17,20}$-lyase inhibitors as an anti-cancer agent include, but are not limited to, hormone ablation agents, anti-androgen agents, differentiating agents, anti-neoplastic agents, kinase inhibitors, anti-metabolite agents, alkylating agents, antibiotic agents, immunological agents, interferon-type agents, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, mitotic inhibitors, matrix metalloprotease inhibitors, genetic therapeutics, and anti-androgens. The amount of the additional anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor. Below are lists of examples of some of the above classes of anti-cancer agents. The examples are not all inclusive and are for purposes of illustration and not for purposes of limitation. Many of the examples below could be listed in multiple classes of anti-cancer agents and are not restricted in any way to the class in which they are listed in.

[0045] Suitable hormonal ablation agents include, but are not limited to, androgen ablation agents and estrogen ablation agents. In preferred embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor is administered with a hormonal ablation agent, such as deslorelin, leuprolide, goserelin or triptorelin. Even though throughout this specification and in the claims the phrase "hormonal ablation agent" is written as a singular noun, for example; "a hormonal ablation agent" or "the hormonal ablation agent," the phrase "hormonal ablation agent" should not be interpreted as being limited to the inclusion of a single hormonal ablation agent. The amount of the hormonal ablation agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0046] Suitable anti-androgen agents include but are not limited to bicalutamide, flutamide and nilutamide. The amount of the anti-androgen agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0047] In another embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor may be administered with a differentiating agent. Suitable differentiating agents include, but are not limited to, polyamine inhibitors; vitamin D and its analogs, such as, calcitriol, doxercalciferol and seocalcitol; metabolites of vitamin A, such as, ATRA, retinoic acid, retinoids; short-chain fatty acids; phenylbutyrate; and nonsteroidal anti-inflammatory agents. The amount of the differentiating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0048] In another preferred embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor may be administered with an anti-neoplastic agent, including, but not limited to, tubulin interacting agents, topoisomerase inhibitors and agents, acitretin, alstonine, amonafide, amphethinile, amsacrine, ankinomycin, anti-neoplaston, aphidicolin glycinate, asparaginase, baccharin, batracylin, benfluron, benzotript, bromofosfamide, caracemide, carmethizole hydrochloride, chlorsulfaquinoxalone, clanfenur, claviridenone, crisnatol, curaderm, cytarabine, cytocytin, dacarbazine, datelliptinium, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, docetaxel, elliprabin, elliptinium acetate, epothilones, ergotamine, etoposide, etretinate, fenretinide, gallium nitrate, genkwadaphnin, hexadecylphosphocholine, homoharringtonine, hydroxyurea, ilmofosine, isoglutamine, isotretinoin, leukoregulin, lonidamine, merbarone, merocyanlne derivatives, methylanilinoacridine, minactivin, mitonafide, mitoquidone, mitoxantrone, mopidamol, motretinide, N-(retinoyl)amino acids, N-acylated-dehydroalanines, nafazatrom, nocodazole derivative, ocreotide, oquizanocine, paclitaxel, pancratistatin, pazelliptine, piroxantrone, polyhaematoporphyrin, polypreic acid, probimane, procarbazine, proglumide, razoxane, retelliptine, spatol, spirocyclopropane derivatives, spirogermanium, strypoldinone, superoxide dismutase, teniposide, thaliblastine, tocotrienol, topotecan, ukrain, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, and withanolides. The amount of the anti-neoplastic agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0049] The 17α-hydroxylase/$C_{17,20}$-lyase inhibitors may also be used with a kinase inhibitor including p38 inhibitors and CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, SOD mimics or $\alpha_v\beta_3$ inhibitors. The amount of the kinase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0050] In another embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor may be administered with an anti-metabolite agent. Suitable anti-metabolite agents may be selected from, but not limited to, 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, doxifluridine, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, isopropyl pyrrolizine, methobenzaprim, methotrexate, norspermidine, pentostatin, piritrexim, plicamycin, thioguanine, tiazofurin, trimetrexate, tyrosine kinase inhibitors, and uricytin. The amount of the anti-metabolite agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0051] In another embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor may be administered with an alkylating agent. Suitable alkylating agents may be selected from, but not limited to, aldo-phosphamide analogues, altretamine, anaxirone, bestrabucil, budotitane, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyplatate, diphenylspiromustine, diplatinum cytostatic, elmustine, estramustine phosphate sodium, fotemustine, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, oxaliplatin, prednimustine, ranimustine, semustine, spiromustine, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol. The amount of the alkylating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0052] In another preferred embodiment, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor may be administered with an antibiotic agent. Suitable antibiotic agents may be selected from, but not limited to, aclarubicin, actinomycin D, actinoplanone, adriamycin, aeroplysinin derivative, amrubicin, anthracycline, azino-mycin-A, bisucaberin, bleomycin

sulfate, bryostatin-1, calichemycin, chromoximycin, dactinomycin, daunorubicin, ditrisarubicin B, dexamethasone, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-Al, esperamicin-Alb, fostriecin, glidobactin, gregatin-A, grincamycin, herbimycin, corticosteroids such as hydrocortisone, idarubicin, illudins, kazusamycin, kesarirhodins, menogaril, mitomycin, neoenactin, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, prednisone, prednisolone, pyrindanycin A, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, sorangicin-A, sparsomycin, talisomycin, terpentecin, thrazine, tricrozarin A, and zorubicin. The amount of the antibiotic agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0053] Alternatively, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitors may also be used with other anti-cancer agents, including but not limited to, acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, amsacrine, anagrelide, anastrozole, ancestim, bexarotene, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, daclizumab, dexrazoxane, dilazep, docosanol, doxifluridine, bromocriptine, carmustine, cytarabine, diclofenac, edelfosine, edrecolomab, eflornithine, emitefur, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, glycopine, heptaplatin, ibandronic acid, imiquimod, iobenguane, irinotecan, irsogladine, lanreotide, leflunomide, lenograstim, lentinan sulfate, letrozole, liarozole, lobaplatin, lonidamine, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mitoguazone, mitolactol, molgramostim, nafarelin, nartograstim, nedaplatin, nilutamide, noscapine, oprelvekin, osaterone, oxaliplatin, pamidronic acid, pegaspargase, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, porfimer sodium, raloxifene, raltitrexed, rasburicase, rituximab, romurtide, sargramostim, sizofiran, sobuzoxane, sonermin, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, ubenimex, valrubicin, verteporfin, vinorelbine. The amount of the anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0054] The 17α-hydroxylase/$C_{17,20}$-lyase inhibitors may also be administered or combined with steroids, such as corticosteroids or glucocorticoids. The 17α-hydroxylase/$C_{17,20}$-lyase inhibitors and the steroid may be administered in the same or in different compositions. Non-limiting examples of suitable steroids include hydrocortisone, prednisone, or dexamethasone. The amount of the steroid administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0055] In one embodiment, provided herein are methods and compositions comprising both abiraterone acetate and a steroid particularly a corticosteroid, or more particularly a glucocorticoid. Steroids within the scope of the disclosure include, but are not limited to, (1) hydrocortisone (cortisol; cyprionate (*e.g.*, CORTEF), oral; sodium phosphate injection (HYDROCORTONE PHOSPHATE); sodium succinate (*e.g.*, A-HYDROCORT, Solu-CORTEF); cortisone acetate oral or injection forms, etc.), (2) dexamethasone (*e.g.*, Decadron, oral; Decadron-LA injection, etc.), (3) prednisolone (*e.g.*, Delta-CORTEF, prednisolone acetate (ECONOPRED), prednisolone sodium phosphate (HYDELTRASOL), prednisolone tebutate (HYDELTRA-TBA, etc.)), or (4) prednisone (*e.g.*, DELTASONE, etc.) and combinations thereof. See, *e.g.*, GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10TH EDITION 2001.

[0056] In a specific embodiment, single unit solid oral dosage forms which comprise an amount from about 50 mg to about 300 mg of abiraterone acetate and an amount from about 0.5 mg to about 3.0 mg of a steroid, *e.g.*, glucocorticoid in a single composition, optionally with excipients, carriers, diluents, etc. is contemplated. For instance, the single unit dosage form can comprise about 250 mg of abiraterone acetate and about 1.0 mg, 1.25 mg, 1.5 mg, or 2.0 mg of a steroid, such as but not limited to corticosteroids or glucocorticoids.

Administration of the 17α-hydroxylase/$C_{17,20}$-lyase Inhibitor and an Additional Therapeutic Agent

[0057] The 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and the additional therapeutic agent, such as an anti-cancer agent or a steroid can be administered by any method known to one skilled in the art. In certain embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and the additional therapeutic agent can be in separate compositions prior to administration.

In the alternative, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and the additional therapeutic agent can be combined into a single composition for administration.

[0058] The 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and the additional therapeutic agent can be administered sequentially or simultaneously. If administered sequentially, the order of administration is flexible. For instance, 17α-hydroxylase/$C_{17,20}$-lyase inhibitor acetate can be administered prior to administration of the additional therapeutic agent. Alternatively, administration of the additional therapeutic agent can precede administration of 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

[0059] Whether they are administered as separate compositions or in one composition, each composition is preferably pharmaceutically suitable for administration. Moreover, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and the therapeutic agent, if administered separately, can be administered by the same or different modes of administration. Examples of modes of administration include parenteral (*e.g.*, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, intradermal, intraperitoneal, intraportal, intra-arterial, intrathecal, transmucosal, intra-articular, and intrapleural,), transdermal (*e.g.*, topical), epidural, and mucosal (*e.g.*, intranasal) injection or infusion, as well as oral, inhalation, pulmonary, and rectal administration. In specific embodiments, both are oral.

[0060] For example, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can be administered transdermally and the additional therapeutic agent can be administered parenterally. Alternatively, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can be administered orally, such as in a tablet, caplet or capsule, while the additional therapeutic agent can be administered intravenously. Such intravenous administered therapeutic agents include, but are not limited to, docetaxel injections, such as Taxotere®; paclitaxel injections, such as Paclitaxel® and mitoxantrone injections, such as Novantrone®. Also, the additional therapeutic agent can be in the form of depots or implants such as leuprolide depots and implants, *e.g.* Viadur® and Lupron Depot®; triptorelin depots, *e.g.* Trelstar®; goserelin implants, *e.g.* Zoladex®.

[0061] The suitable daily dosage of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor depends upon a number of factors, including, the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, and response of the individual patient. Suitable daily dosages of 17α-hydroxylase/$C_{17,20}$-lyase inhibitors can generally range from about 0.0001 mg/kg/day to about 1000 mg/kg/day, or

from about 0.001 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 200 mg/kg/day, or from about 0.01 mg/kg/day to about 100 mg/kg/day in single or multiple doses.

[0062] In some embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can be administered in an amount from about 0.004 mg/day to about 5,000 mg/day, or from about 0.04 mg/day to about 3,000 mg/day, or from about 0.4 mg/day to about 1500 mg/day. In certain embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can be administered in an amount from about 0.1 mg/day to about 2000 mg/day or from about 1 mg/day to about 2000 mg/day or from about 50 mg/day to about 2000 mg/day or from about 100 mg/day to about 1500 mg/day or from about 5 mg/day to about 1,000 mg/day or from about 5 mg/day to about 900 mg/day or from about 10 mg/day to about 800 mg/day or from about 15 mg/day to about 700 mg/day or from about 20 mg/day to about 600 mg/day or from about 25 mg/day to about 500 mg/day in single or multiple doses.

[0063] In certain embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor is co-administered with an additional anti-cancer agent such as mitoxantrone, paclitaxel or docetaxel. For example, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of mitoxantrone. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the mitoxantrone can be administered in an amount of about 0.1 mg/m^2 to about 20 mg/m^2. Preferably, the mitoxantrone is administered over a period of between about 10 to about 20 minutes once every 21 days.

[0064] Also, a method for the treatment of a cancer in a mammal can comprise administering an amount of abiraterone acetate and an amount of paclitaxel. In one embodiment, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the paclitaxel can be administered in the amount of about 1 mg/m^2 to about 175 mg/m^2. Preferably, the paclitaxel is administered over a period of between about 2 to about 5 hours once every three months.

[0065] Additionally, a method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of docetaxel. For example, the abiraterone acetate can be administered in an amount of about 0.01 mg/kg/day to about 100 mg/kg/day and the docetaxel can be administered in an amount of about 1 mg/m^2 to about 100 mg/m^2. Preferably, the docetaxel is administered over a period of between about 1 to about 2 hours once every three weeks.

[0066] In certain embodiments, the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor is administered along with an anti-cancer agent that comprises a hormonal ablation agent, including, but not limited to, leuprolide, goserelin, or triptorelin. For example, one method for the treatment of a cancer in a mammal also comprises administering an amount of abiraterone acetate and an amount of leuprolide. The amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of leuprolide can be about 0.01 mg to about 200 mg over a period of about 3 days to about 12 months. Preferably, the leuprolide is administered in the amount of about 3.6 mg of leuprolide over a period of about 3 days to about 12 months.

[0067] Additionally, the methods for the treatment of cancer in a mammal include administering an amount of abiraterone acetate and an amount of goserelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of goserelin can be about 0.01 mg to about 20 mg over a period of about 28 days to about 3 months. Preferably, the goserelin is administered in the amount of about 3.6 mg to about 10.8 mg over a period of about 28 days to about 3 months.

[0068] In certain embodiments the methods for the treatment of cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of triptorelin. For example, the amount of abiraterone acetate can be about 0.01 mg/kg/day to about 100 mg/kg/day and the amount of triptorelin can be about 0.01 mg to about 20 mg, over a period of about 1 month, preferably the triptorelin is administered in the amount of about 3.75 mg over a period of about 1 month.

[0069] Also, in one embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of seocalcitol. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 μg/day to about 500 μg/day of seocalcitol, such as about 100 μg/day of seocalcitol.

[0070] In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of bicalutamide. For instance, the method involves administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

[0071] In yet another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of abiraterone acetate and an amount of

flutamide. For example, the method comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

[0072] Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor such as abiraterone acetate and an amount of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of hydrocortisone. In other instances, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of hydrocortisone.

[0073] The method for the treatment of a cancer can also comprise administering an amount of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as prednisone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of prednisone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 10 mg/day to about 250 mg/day of prednisone.

[0074] In addition, the method for the treatment of a cancer can also comprise administering an amount of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate, and an amount of a glucocorticoid, such as dexamethasone. For example, the method can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of dexamethasone. Also, the method can comprise administering an amount of about 500 mg/day to about 1500 mg/day of abiraterone acetate and an amount of about 0.5 mg/day to about 25 mg/day of dexamethasone.

Compositions Containing a 17α-hydroxylase/$C_{17,20}$-lyase Inhibitor and an Additional Therapeutic Agent

[0075] In certain embodiments, the compositions can contain a combination of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, preferably abiraterone acetate, and any of the therapeutic agents recited above. Whether the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and

the additional therapeutic agent are administered in separate compositions or as a single composition, the compositions can take various forms. For example, the compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders or sustained-release formulations, depending on the intended route of administration.

[0076] For topical or transdermal administration, the compositions can be formulated as solutions, gels, ointments, creams, suspensions or salves.

[0077] For oral administration, the compositions may be formulated as tablets, pills, dragees, troches, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0078] The composition may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas that contain conventional suppository bases such as cocoa butter or other glycerides.

[0079] In addition to the formulations described previously, the composition may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the therapeutic agents may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0080] Additionally, the composition may be delivered using a sustained-release system, such as semi-permeable matrices of solid polymers containing the composition. Various forms of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature can release the composition over a period of hours, days, weeks, months. For example a sustained release capsule can release the compositions over a period of 100 days or longer. Depending on the chemical nature and the biological stability of the composition, additional strategies for stabilization may be employed.

[0081] The compositions can further comprise a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered.

[0082] For parenteral administrations, the composition can comprise one or more of the following carriers: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial

agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

[0083] For oral solid formulations suitable carriers include fillers such as sugars, *e.g.*, lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, fats and oils; granulating agents; and binding agents such as microcrystalline cellulose, gum tragacanth or gelatin; disintegrating agents, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate, Primogel, or corn starch; lubricants, such as magnesium stearate or Sterotes; glidants, such as colloidal silicon dioxide; a sweetening agent, such as sucrose or saccharin; or flavoring agents, such as peppermint, methyl salicylate, or orange flavoring. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

[0084] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy injectability with a syringe. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars; polyalcohols such as mannitol, sorbitol; sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0085] Also for intravenous administration, the compositions may be formulated in solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In a preferred embodiment, the compositions are formulated in sterile solutions.

[0086] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

[0087] For administration by inhalation, the compositions may be formulated as an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the composition and a suitable powder base such as lactose or starch.

[0088] The pharmaceutical compositions may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0089] One example of a composition comprising a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and an additional therapeutic agent is an oral composition or composition suitable for oral administration comprising abiraterone acetate in combination with a steroid. For example, the oral composition can be a solid dosage form such as a pill, a tablet or a capsule. The oral composition can comprise about 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg of abiraterone acetate. The oral composition can comprises about 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 7.5 mg, 10 mg, 20 mg, 30 mg, 40 mg or 50 mg of a steroid, such as a glucocorticoid.

[0090] In one embodiment, the oral composition can comprise about 50 mg to about 500 mg of abiraterone acetate and an amount of about 0.25 mg to about 3.5 mg of the

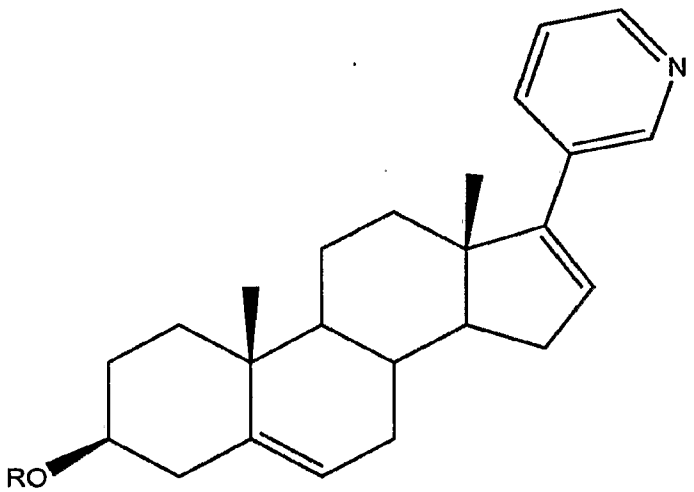
steroid, such as hydrocortisone, prednisone or dexamethasone. In other instances, the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and an amount of about 1.0 mg to about 2.5 mg of the steroid, such as hydrocortisone, prednisone or dexamethasone. In another embodiment the composition can comprise about 50 mg to about 300 mg of abiraterone acetate and about 0.5 mg to about 3.0 mg of a steroid. For example, the oral composition can be a tablet containing 250 mg of abiraterone acetate; 1.25 mg or 2.0 mg of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients. Additionally, the oral composition can be a capsule containing 250 mg of abiraterone acetate; 1.25 mg or 2.0 mg of a steroid, such as hydrocortisone, prednisone or dexamethasone; and one or more carriers, excipients, diluents or additional ingredients.

[0091] The description contained herein is for purposes of illustration and not for purposes of limitation. The methods and compositions described herein can comprise any feature described herein either alone or in combination with any other feature(s) described herein. Changes and modifications may be made to the embodiments of the description. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

THE CLAIMS

What is claimed is:

1. A method for the treatment of a cancer in a mammal comprising administering a therapeutically effective amount of at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and a therapeutically effective amount of at least one additional therapeutic agent to a patient having a cancer; wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises a compound of the formula (I) or an analog, a derivative, a metabolite or a pharmaceutically acceptable salt thereof,



(I)

wherein R represents a hydrogen, or an acyl group having 1-4 carbons.

2. The method of claim 1, wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises abiraterone acetate or an analog, a derivative, a metabolite or a pharmaceutically acceptable salt thereof.

3. The method of claim 2, wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises the mesylate salt of abiraterone acetate.

4. The method of claim 1, wherein the therapeutically effective amount of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 50 mg/day to about 2000 mg/day.

5. The method of claim 1, wherein the additional therapeutic agent comprises an anti-neoplastic agent, an alkylating agent, an anti-metabolite agent, an antibiotic agent, a hormonal ablation agent, an androgen ablation agent, an anti-androgen agent, or a steroid.

6. The method of claim 1, wherein the additional therapeutic agent comprises mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, hydrocortisone, prednisone or dexamethasone.

7. The method of claim 1, wherein the 17α-hydroxylase/$C_{17,20}$ lyase inhibitor and the additional therapeutic agent are administered to the mammal in a single composition comprising the 17α-hydroxylase/$C_{17,20}$ lyase inhibitor and the additional therapeutic agent.

8. The method of claim 1, wherein the 17α-hydroxylase/$C_{17,20}$ lyase inhibitor and the additional therapeutic agent are administered separately to the mammal.

9. The method of claim 1, wherein the cancer is prostate cancer or breast cancer.

10. The method of claim 1, wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 0.1 mg/m^2 to about 20 mg/m^2 of mitoxantrone.

11. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 1 mg/m^2 to about 175 mg/m^2 of paclitaxel.

12. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 1 mg/m^2 to about 100 mg/m^2 of docetaxel.

13. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100

mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 0.01 to about 200 mg of leuprolide over a period of about 3 days to about 12 months.

14. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 20 mg of goserelin over a period of about 28 days to about 3 months.

15. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 0.01 mg to about 20 mg of triptorelin over a period of about 1 month.

16. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 0.1 μg/day to about 500 μg/day of seocalcitol.

17. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 1 mg/day to about 300 mg/day of bicalcutamide.

18. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 1 mg/day to about 2000 mg/day flutamide.

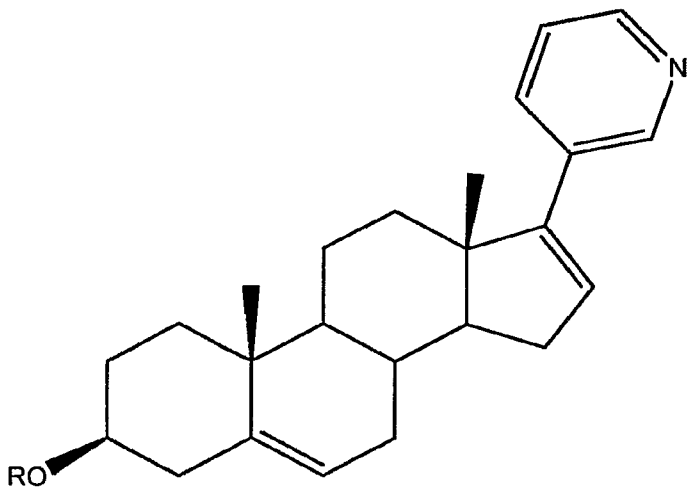
19. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 50 mg/day to about 2000 mg/day of abiraterone acetate and the therapeutically effective amount of the at least one

additional therapeutic agent comprises about 10 mg/day to about 250 mg/day of hydrocortisone.

20. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 50 mg/day to about 2000 mg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 10 mg/day to about 250 mg/day prednisone.

21. The method of claim 1 wherein the therapeutically effective amount of the at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 50 mg/day to about 2000 mg/day of abiraterone acetate and the therapeutically effective amount of the at least one additional therapeutic agent comprises about 0.5 mg/day to about 25 mg/day dexamethasone.

22. A method for treating a patient having a refractory prostate or breast cancer who is currently receiving at least one treatment for cancer, the method comprising administering a therapeutically effective amount of at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor in addition to the at least one treatment the patient is currently receiving, wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises a compound of the formula (I) or an analog, a derivative, a metabolite or pharmaceutically acceptable salt thereof,



(I)

wherein R represents a hydrogen, or an acyl group having 1-4 carbons.

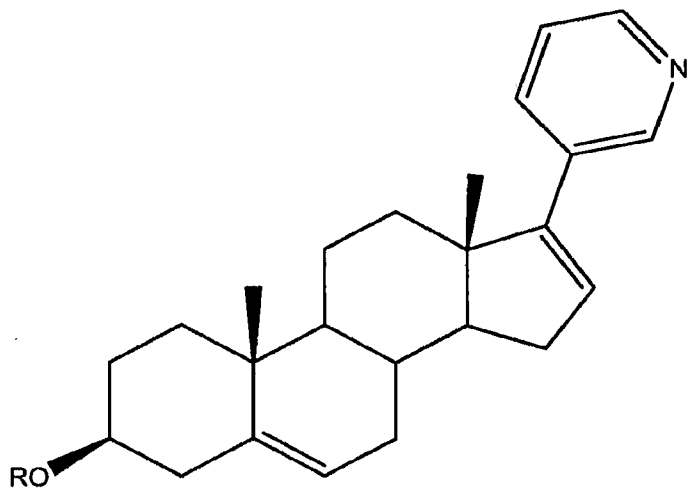
23. The method of claim 22, wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises abiraterone acetate or an analog, a derivative, a metabolite or a pharmaceutically acceptable salt thereof.

24. The method of claim 23, wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises the mesylate salt of abiraterone acetate.

25. The method of claim 22, wherein the therapeutically effective amount of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 50 mg/day to about 2000 mg/day.

26. The method of claim 22, wherein the treatment for cancer comprises the administration of an anti-cancer agent, chemotherapy, radiation or surgery.

27. A pharmaceutical composition for the treatment of a cancer in a mammal comprising a therapeutically effective amount of at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor; and at least one additional therapeutic agent; wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises a compound of the formula (I) or an analog, a derivative, a metabolite or a pharmaceutically acceptable salt thereof,



(I)

wherein R represents a hydrogen, or an acyl group having 1-4 carbons.

28. The composition of claim 27, wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises abiraterone acetate or an analog, a derivative, a metabolite or a pharmaceutically acceptable salt thereof.

29. The composition of claim 28, wherein the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises the mesylate salt of abiraterone acetate.

30. The composition of claim 27, wherein the therapeutically effective amount of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor comprises about 50 mg to about 500 mg.

31. The composition of claim 27, wherein the additional therapeutic agent comprises mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, hydrocortisone, prednisone or dexamethasone.

32. A pharmaceutical composition for the treatment of a cancer in a mammal comprising a therapeutically effective amount of abiraterone acetate; and a therapeutically effective amount of a steroid, wherein the composition is suitable for oral administration.

33. The composition of claim 32 wherein the composition is a solid dosage form.

34. The composition of claim 32, wherein the composition comprises about 50 mg to about 500 mg of abiraterone acetate, and about 0.25 mg to about 3.5 mg of the steroid.

35. The composition of claim 32, wherein the steroid comprises hydrocortisone, prednisone, or dexamethasone.

36. The composition of claim 32, wherein the composition is in the form of a pill, tablet or capsule.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/018769

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 A61K31/58 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, CHEM ABS Data, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	O'DONNELL A ET AL: "Hormonal impact of the 17[alpha]-hydroxylase/C17,20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer" BRITISH JOURNAL OF CANCER 14 JUN 2004 UNITED KINGDOM, vol. 90, no. 12, 14 June 2004 (2004-06-14), pages 2317-2325, XP002464868 ISSN: 0007-0920 page 2318, right-hand column, paragraph 1 page 2319, left-hand column, paragraph 7 - right-hand column, paragraph 13 page 2320, right-hand column, paragraph 2 page 2323, right-hand column, paragraph 4 ----- -/--	1,2,4-6, 9,22,23, 25-28, 30-32,35

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 January 2008	28/01/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/018769

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/037269 A (PANTARHEI BIOSCIENCE B V [NL]; COELINGH BENNINK HERMAN JAN TI [NL]; BU) 6 May 2004 (2004-05-06) claims 14-19 page 12, line 11 - page 13, line 32	1,2,5, 7-9,27, 28,32, 33,36
X	US 2006/030608 A1 (NELSON RICHARD M [US] ET AL) 9 February 2006 (2006-02-09) paragraph [0186] paragraph [0197] paragraph [0241] paragraph [0191] paragraph [0193] paragraph [0196]	1,2,5,7, 8,27,28
X	WO 02/053138 A (SHANAHAN-PRENDERGAST ELISABETH [IE]) 11 July 2002 (2002-07-11) claims 1,7-9 page 12, line 20 - page 13, line 31 page 14, line 29 - page 19, line 25 page 16, line 30 page 21, line 9 - page 22, line 21	1,2,5,7, 8,27,28
A	WO 2006/021776 A (BTG INT LTD [GB]; HUNT NEIL JOHN [GB]) 2 March 2006 (2006-03-02) cited in the application	
A	MADAN RAVI A ET AL: "Abiraterone Cougar Biotechnology" IDRUGS, CURRENT DRUGS LTD, GB, vol. 9, no. 1, 2006, pages 49-55, XP008087480 ISSN: 1369-7056	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-26 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/018769

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

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

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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

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

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

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

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

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

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

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

Remark on Protest

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

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/018769

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004037269 A	06-05-2004	AT 380552 T	15-12-2007
		AU 2003274823 A1	13-05-2004
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